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THE EFFECT OF VACCINE ON CANCER PATIENTS

JOHN B. GRAHAM, M.D., F.A.C.S., and RUTH M. GRAHAM, Sc.D.,
Buffalo, New York

CANCER VACCINES have been given in an effort to bolster the patient's resistance to cancer. Vaccine prepared from the individual's own tumor and Freund's adjuvant (1) has been tried in a series of patients with advanced cancer. Some of the patients may have been benefited. The majority have not.

The introduction of tumor vaccine is based upon the hypothesis that some part of the tumor is antigenically different from the host and that host resistance is important in human cancer.

Interest in the immune treatment of cancer was aroused by Jensen, who observed that a transplantable mouse carcinoma could be caused to regress and disappear if treated with an immune rabbit serum. This stimulated von Leyden and Blumenthal to repeat the work on dogs and then to go on to an attempt on active immunity by repeated injection of the juice expressed from the individual's own tumor. This was tried successfully on a dog with a carcinoma of the rectum, and then on 3 patients, 2 of whom seemed improved. That report appeared in 1902. In the ensuing years, numerous attempts were made using a variety of autolysates, cell-free extracts, attenuated cells, and intact cells from the patient's own tumor or a similar tumor with indifferent results. Most reports had some encouraging features, but they were not convincing and apparently were abandoned after a brief trial. More recently, Stone and his colleagues have implanted bits of tumor killed by freezing or exposure to ethylene oxide, and again the results are inconclusive.

Although animals can be readily immunized against subsequent implants of transplantable tumors, we are aware of no experiments in which an established tumor is consistently and successfully treated by a vaccine. This failure is due in part to the rapid course run by most transplantable and spontaneous tumors in animals. And it has discouraged work in patients, in spite of the verity attributed to Wassermann—"Mausekrebs ist kein Menschenkrebs." Two weaknesses have plagued human experiments and, to a large extent, the animal experiments as well. First, there has been no measurement except clinical course, which is notoriously difficult to evaluate and which may totally obscure significant but less striking effects. Secondly, the vaccine in each case has been either whole tumor, a fraction, or a product of the tumor, all of which are presumably found in the cancer patient and

From the Roswell Park Memorial Institute, Buffalo, New York.

have been incapable of spontaneously eliciting the desired response. It is evident that one must offer either a more antigenic preparation of the tumor or change the patient so that he is more reactive. The present studies follow the former line by introducing adjuvants with the tumor antigen.

An adjuvant is an agent that helps the antigen elicit a more vigorous immune response. With adjuvants, the immune process can be enhanced so tremendously that the individual will damage or destroy his own uveal tract, nervous tissue, testicular germinal epithelium, or thyroid. If a destructive immunity can be elicited and directed against normal tissues, it seems reasonable to assume that a similar and more vigorous response could be produced against a cancer which already shows some evidence of antigenicity.

A variety of adjuvants have been proposed, including staphylococcus toxin, killed nonhemolytic streptococci, mineral oil, and killed tubercule bacilli. The most potent is a combination, devised by Freund, of a light mineral oil, and emulsifying agent (arlacel A), and killed mycobacteria (3). It is mixed with equal parts of the antigen to produce a water-in-oil emulsion. With this adjuvant, the immune response to a standard antigen such as killed typhoid bacilli is 20-fold greater than with the bacilli alone and is maintained at high levels for many months (2). Freund's adjuvant has been notably successful in eliciting an immune response to the individual's own tissues; i.e., nerve, testis, and thyroid. Because of the potency of Freund's adjuvant, there has been some reluctance in applying it in patients for fear of untoward side reactions such as the development of neuritis, or encephalitis. The emulsifying agent, arlacel A and/or mineral oil, has been used successfully in influenza vaccine in hundreds and thousands of humans without serious complications. In one group of 6,000 there was a 1 per cent incidence of cyst formation at the injection site attributed to impurities in the arlacel. There has been no large scale use in humans of the complete Freund's adjuvant containing killed mycobacteria. However, Witebsky (8) had used it with a saline extract of the tumor in a half dozen cancer patients without complication.

Freund's adjuvant may not be as effective when prepared with Mycobacterium butyricum as with Mycobacterium tuberculosis; but, it is safer to use the former in order to avoid possible complication of a pre-existing tubercular process. The complete adjuvant with mycobacteria is preferably given only once, because subsequent inoculations may invite an intense response to the mycobacterial protein. However, a second injection containing mineral oil and arlacel devoid of acid fast bacilli may be given with less risk. The wax of the mycobacteria is regarded as the active constituent and theoretically can be used in the preparation of subsequent inocula without the undesirable side effect of the protein in the whole bacteria. Although the wax preparations are effective, there is doubt that they are as potent as the whole killed bacilli.

From experience in animals, the intradermal route is regarded as the most effective route of administration of a vaccine made with Freund's adjuvant. However, it usually results in a local ulceration. The intramuscular route is somewhat less effective, but well tolerated. Subcutaneous injections lead to abscess formation.

Experience with well-known infectious diseases has shown that the most effective immunization is conferred by the introduction of the living unattenuated organism, the attentuated organism is somewhat less effective, and the killed organism or its products is only active in certain instances; e.g., typhoid or diphtheria. These observations have influenced the approach to tumor vaccines.

Use of the living unattenuated tumor was an attractive but disappointing approach, for surgeons have long known that one may transfer a piece of tumor from one site to another in the same patient and it will grow there. However, in the laboratory it was known that if a transplantable tumor grew for a time and then regressed the animal was

immune to additional inoculations of that tumor. Intracutaneous administration of transplantable tumors was found to result in more frequent regression and immunity in animals but failed in an experiment in a patient. The cancer cells may be killed by freezing and thawing, but this method is regarded as unreliable, as prolonged survival of tumor has been reported, and autolysis may result. Killing the tumor by heating or chemical means risks altering or destroying the essential antigen. Mechanical destruction of the tumor cell is less likely to destroy the antigen, but must be done under carefully controlled circumstances of asepsis, low temperature, and rapid handling to minimize bacterial contamination and autolysis.

A whole tumor preparation in a vaccine has the advantage of containing all of the ingredients, and it is hoped the body will develop the maximum immune response toward the elements that are most different from those of the host; i.e., the postulated antigen. Possible disadvantages are that the antigen is so dilute that an effective response is impossible, or that the whole tumor contains an inhibitor that prevents the immune response, or that the body will develop an immune response against normal nonmalignant constituents. These disadvantages could be reduced by using a fraction of the tumor. But, what fraction? A variety of fractions have been proposed as containing the essential antigen. These include normal saline, 1 molar sodium chloride, alcohol, and proteose. Normal saline extracts much of the protein, carbohydrate, and a host of metabolites and enzymes, most of the cytoplasm, and part of the nuclear content. One molar sodium chloride will take out the desoxyribose nucleoprotein, including that of a virus if present, as well as other lesser ingredients. Alcohol and proteose remove some lipids or lipid proteins. All of these fractions have had antigenic activity when tested in animals.

METHODS AND MATERIALS

One hundred and fourteen patients received Freund's adjuvant type autogenous vaccines. All had advanced cancer with an unfavorable prognosis. Gynecologic cancer forms the bulk of our material (Table I). Thirteen died within the first month of observation of the disease and are excluded from the following analysis.

TABLE I

Site of tumor	*Patient lived more than 1 month*	*Patient died within 1 month*
Cervix	50	5
Uterine corpus	9	3
Ovary	22	2
Vulva	7	1
Colon	5	
Corpus et cervix	4	
Breast	2	
Pelvic cancer	1	1
Vagina	1	
Uterine sarcoma		1

Four types of antigens were used in the vaccine; i.e., whole tumor homogenate, 1 molar sodium chloride extract, normal saline extract and suspension, and cellular suspension.

The whole tumor homogenate was prepared in a cooled, high speed stirrer by cutting the tissue in small pieces, stirring at low speed with 2 to 3 volumes of normal saline for a minute, and centrifuging. This was repeated until the supernatant was clear. The resulting precipitate consisted largely of nuclei with some connective tissue. This was then homogenized at 45,000 revolutions per minute with 10 volumes of saline until all nuclei were broken, which was verified microscopically. The time of homogenization varies considerably as some tumors are much easier broken than others.

The 1 molar sodium chloride extract was prepared by adding 5 volumes of 1 molar sodium chloride to the nuclear precipitate prepared as described before. This was homogenized at high speed until no intact nuclei could be identified. The material was spun at high speed in a refrigerated centrifuge for one-half hour. The precipitate was disregarded. Distilled water was added to the supernatant to make a sodium chloride concentration of 0.14 mol. The resulting precipitate was removed by centrifugation at

high speed for one-half hour. This represented the normal saline insoluble, 1 molar sodium chloride soluble fraction. Reprecipitation of this fraction was carried out again in most instances by redissolving the precipitate in 1 molar sodium chloride and reprecipitating it by the addition of distilled water. A fine white material was obtained.

The normal saline extract and suspension was made by stirring the tumor with 5 volumes of saline at about 5,000 revolutions per minute in an Osler homogenizer for 30 minutes. After light centrifugation the supernatant was used as antigen. This preparation was largely an extract but also contained some intact nuclei. This antigen was prepared by Dr. Ernest Witebsky's staff at the Buffalo General Hospital.

Because these preparations were not as effective as we had hoped for, we resorted to a fourth antigen preparation—the cellular suspension. This was made by forcing tumor through a fine mesh screen with the gloved finger. The resulting paste was scraped from the under surface of the screen and used. If it was too thick 1 volume of saline was added. The pores of the screen were 0.1 by 0.1 millimeter, and the material obtained consisted of tumor nuclei with varying amounts of attached cytoplasm.

Four forms of Freund's adjuvant were used. The "complete M. butyricum" contained 85 parts of thin mineral oil, cleartek or bayol F, 15 parts arlacel A, and 0.025 per cent killed dried Mycobacterium butyricum. The "complete M. tuberculosis" had the same composition but killed Mycobacterium tuberculosis was substituted for Mycobacterium butyricum. The third preparation substituted purified wax for the killed mycobacteria. The wax was prepared by Dr. R. J. Anderson from Mycobacterium tuberculosis and is active in the induction of hypersensitivity. The concentration of wax was 2 milligrams per cubic centimeter. The fourth preparation was similar to this but devoid of mycobacteria or wax, and it was referred to as "incomplete." The adjuvant was sterilized by autoclaving.

The final step in the preparation of vaccine consisted of slowly adding the antigen to an equal volume of adjuvant while the mixture was repeatedly drawn into and expelled from a syringe to form a milky, water-in-oil emulsion. The resultant emulsion should remain as a single globule when dropped on water. If it spreads out over the surface, further emulsification is necessary.

The volume of injected vaccine varied from 0.1 to 2.0 cubic centimeters and 0.05 to 1.0 cubic centimeter in any site. The intramuscular (gluteal) route was used initially but in 5 out of 25 cold abscesses developed. Subsequently, the intradermal (anterior thigh) route was used. Two sites were injected simultaneously. Fifty-six patients received vaccine only once. Forty-five received it on 2 or more occasions, and the maximum number of injections was 6 in 1 patient.

The patients' clinical course was closely observed and recorded; vaginal or rectal smears were taken regularly for cytologic evaluation. Differential counts were done on the smears to determine the level of the sensitization response, radiation response, and histiocytes. Biopsy specimens were taken in all cases prior to vaccination and subsequently whenever possible. Hemoglobin, white blood counts, and differentials were taken regularly. All patients were treated prior to April 1, 1958 and have been observed for a minimum of 7 months. The first patient was treated in October 1955. Twenty-five patients were treated in the Boston area at the Massachusetts General Hospital, Free Hospital for Women in Brookline, and Pondville Hospital in 1955 and 1956. The remainder have been treated at Roswell Park Memorial Institute.

RESULTS

The results are expressed in terms of survival, cytologic evaluation, and complications. Fifty-five of the 101 patients lived 7 months or more, 8 are living with demonstrable tumor but it is quiescent and they

TABLE II.—CLINICAL EVALUATION OF VARIOUS FACTORS IN PATIENTS WHO RECEIVED AUTOGENOUS VACCINE

	Total No.	No. living 7 months or more	No. living with quiescent disease	No. living and well —no evidence of disease
Site of lesion				
Cervix	50	24	3	8
Uterine corpus	9	5	2	1
Ovary	22	15	3	4
Vulva	7	1	0	1
Miscellaneous	13	10	0	0
	101	55	8	14
Kind of antigen				
Whole tumor homogenate	27	13	1	3
1M NaCl extract	27	10	0	2
Saline extract and suspension	7	2	0	0
Cellular suspension	40	30	7	9
	101	55	8	14
Patient subsequently received				
Palliative radiotherapy	25	11	1	2
Full radiotherapy	33	25	6	5
Chemotherapy	8	4	0	0
No treatment. Tumor previously removed, possibly completely	6	6	0	5
No treatment, gross tumor present	29	9	1	2
	101	55	8	14
No. of injections of vaccine				
1	56	29	7	2
2	32	19	1	12
3 or more	13	7	0	0
	101	55	8	14
Volume of first injection				
0.2 c.c. or less	26	12	0	5
0.3–1.0 c.c.	64	36	6	7
1.1 c.c. or more	11	7	2	2
	101	55	8	14
Route of first injection				
Intramuscular	25	12	1	2
Intradermal	66	34	5	10
Intradermal and intracervical	10	9	2	2
	101	55	8	14
Electrophoresis				
Increase of gamma-globulin 3 times standard deviation or more	6	5	2	0
Gamma-globulin change less than above	29	23	1	5
Not done	66	27	5	9
	101	55	8	14
Ulceration of vaccine site				
Yes	63	42	7	13
No	12	2	0	0
No intradermal injection	26	11	1	1
	101	55	8	14
Sensitization response				
SR increased 20 per cent or more	26	18 (69%)	0	5 (19%)
SR changed less than above	40	21 (52%)	5	3 (7%)
Cytology not suitable	35	16	3	6
Histiocytes				
Increased 25 per cent or more	17	13 (76%)	1	4
Changed less than above	33	20	4	3
Not suitable	51	22	3	7

are able to live usefully in comfort. Fourteen are living and well with no demonstrable disease. The site of tumor does not seem to influence the result. The patients who subsequently received full radiotherapy (3,000 r or more, tumor dose, 3 to 4 weeks post vaccine) present better results than either palliative radiotherapy (less than 3,000 r, 3 to 4 weeks post vaccine) or chemotherapy. However, patients who were given full radiotherapy tend to have a better prognosis than the other two groups under ordinary circumstances. The patients with possibly complete excision of tumors had extensive disease that was removed with a narrow margin. The surgeon had doubt as to the completeness of removal, and vaccine was given prophylactically. Five of the 6 continue to show no evidence of recurrence.

Twenty-nine patients in whom gross tumor was present at the time vaccine was given received no further treatment. Two of these have no demonstrable disease and another is living with quiescent tumor.

Preparation of the vaccine. The best preparation of the antigen for vaccine appears to be the cellular suspension, for three-quarters of the patients lived 7 months or longer. Whole tumor homogenate, 1 molar sodium chloride extract, and normal saline extract and suspension followed in that order of apparent effectiveness.

Number of injections. We have no data on the relative effectiveness of the adjuvants. Complete adjuvants, i.e., those containing killed mycobacteria, were used in all first injections.

Fifty-six patients were given an injection on only 1 occasion. In 32, it was repeated once and, in 13, 3 or more injections were given. Those who received injections on 2 occasions, 1 month or more apart, seemed to obtain the best results, for 12 of those free of disease were found in that category.

Volume of injection. The volume of vaccine given does not appear to be of great importance. The intradermal route may be better than the intramuscular, but there is no great difference in the survival rate. However, it is interesting that 9 out of 10 to whom the vaccine was given in the cervix as well as the skin of the anterior thighs lived for 7 months or more.

Electrophoresis. Electrophoretic patterns of the serum were made of 35 patients. After vaccination, 6 showed a rise in gamma globulin of more than 3 times the standard deviation. There was no correlation with clinical effect. Actually, we had made this test to observe possible nephrosis-like effect, but there was nothing about the serum protein pattern to suggest that or any other complication.

Ulceration at vaccine site. Sixty-three out of 75 had an ulceration at the vaccine site after intradermal injection. The 12 who had no ulceration had a less favorable course than the others.

Cytology. The level of histiocytes and of sensitization response cells in the vaginal smears was observed in patients who had had no radiotherapy within 1 month before or after vaccine. It may be recalled that sensitization response (SR) cells are epithelial cells with dense staining finely vacuolated cytoplasm (4). When SR cells are present in significant numbers (10 per cent) in cancer of the cervix patients prior to treatment they indicate a favorable prognosis to radiotherapy. Twenty-six of 60 patients showed an increase of 20 per cent or more SR cells after vaccine. These showed a slightly better survival rate and symptom-free rate. Histiocytes were evaluated in 50 patients and 17 showed a rise of 25 per cent or more after vaccine. Thirteen (76 per cent) of these 17 survived 7 months, and 4 were free of disease, suggesting a somewhat more favorable prognosis than was found in the patients whose histiocytes failed to increase that much. The total number in whom cytology is recorded here is limited not only by irradiation near the time of injection but also by other factors such as fistulas and technically inadequate smears.

Hematology. White blood counts were performed on the peripheral blood and found to vary from normal to as high as 29,000 per cubic millimeter. The usual postvaccine level was from 10,000 to 20,000 per cubic millimeter. The differential count was unremarkable aside from an eosinophilia in about a third of the patients. The maximum level was 39 per cent. The leucocyte level did not seem to correlate with the clinical course.

ABSTRACTS OF PATIENTS IN WHOM GROSS TUMOR WAS PRESENT AT TIME OF VACCINATION AND NO FURTHER TREATMENT WAS GIVEN

M. C., a 52 year old woman, had a recurrent squamous cancer of the cervix in October 1957. Two years before, a stage I lesion was treated with adequate radiotherapy. One year later, a suburethral metastasis was treated with radium needles, and retreated with radium needles 6 months later. In August 1957, an anterior exenteration was done. On October 23, a biopsy of the area beneath the symphysis pubis was positive, and on October 25 gross tumor was found in the excavation above the vaginal orifice, and a node, about the size of a hen's egg, containing tumor was removed from the left groin. SR was 21 per cent. Vaccine prepared from the metastatic node was given on that date (cellular suspension, Freund's with M. tuberculosis, 0.4 c.c. intradermally in each of 2 sites on the anterior thighs). In January 1958, a 5 by 3 centimeter tumor in the clitoral area had developed, and an enlarged left inguinal node was palpable. SR was 60 per cent. On January 28, the vulval tumor was locally excised and vaccine was given. Cellular suspension (Freund's with M. butyricum, 0.2 c.c. intradermally in each thigh). Three months later, there was no palpable tumor, the patient felt well, and her SR was 55 per cent. In September 1958, the patient was well with no evidence of disease. No treatment had been

applied to the proved subsymphysial tumor that encircled the orifice left by exenteration and only 1 node was removed from the left groin as a biopsy to furnish tumor for vaccine.

M. P., a 64 year old woman, had a 1.5 centimeter lesion of the right labia minora treated by radical vulvectomy in March 1957. In November 1957, she returned with a recurrence involving the urethral meatus and the right vaginal wall. On November 26, 1957, the tumor was partially excised leaving gross disease in the right paravaginal region. Vaccine was given (cellular suspension, Freund's with M. tuberculosis 0.25 c.c. intradermally in each anterior thigh). In September 1958, the patient had no demonstrable tumor. Urinary incontinence due to scarring of the internal sphincter was her only complaint.

R. M., a 56 year old woman, underwent an exploratory laparotomy with biopsy of the omentum on October 3, 1955. A 7 centimeter tumor mass in the pelvis and extensive tumor of the peritoneal surfaces including the liver surface were undisturbed. X-ray therapy from November 7, 1955 to January 5, 1956 consisting of 3,200 roentgen depth dose was given. On March 26, 1956, she was readmitted to the hospital, debilitated, with a large mass in the pelvis. Vaccine was given on March 27, 1956 (whole tumor homogenate, Freund's adjuvant with M. butyricum, 0.5 c.c. intramuscularly). She was discharged for terminal care. In October 1956, she was found to feel well with no symptoms. A large pelvic mass rising 4 fingers' breadth above the pubis was palpated. On December 27, 1956, a "second look" laparotomy was performed. Numerous nodules ranging up to 1 centimeter were found over the peritoneal surfaces and a biopsy was made of 1. The mass in the pelvis involved numerous loops of bowel and was not disturbed. Histologic report on the excised nodule was "fat necrosis." In July 1958, she was feeling well and the pelvic mass was unchanged. She was leading an active, normal life.

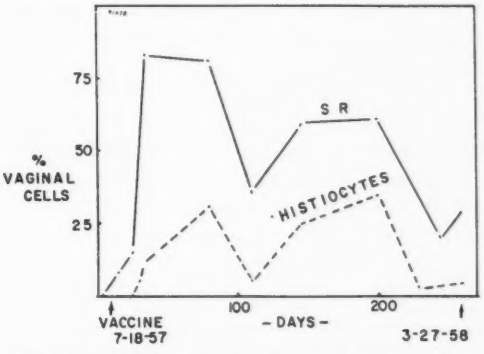

FIG. 1. Vaginal cytologic response after subtotal excision of medullary carcinoma of the ovary and injection of vaccine. Note the rise in both SR and histiocytes that was associated with a feeling of well being without symptoms. The drop in both SR and histiocytes coincided with clinical recurrence.

COMPLICATIONS

The vaccine was given intramuscularly in 25 patients, and in 5 cold abscesses developed that opened and drained over a period of several months. For that reason and because the intradermal route offered some possible theoretic advantage all subsequent patients had intradermal administration. As mentioned previously, in 84 per cent ulceration developed at the injection site that was tender and healed slowly over a period of from 3 to 4 months. In 2 patients of the 40 receiving cellular suspension, implants developed at the vaccine site. In 1, this occurred 2 weeks prior to death from advancing uncontrolled cancer of the vulva. The other occurred as a satellite nodule 2 centimeters distal to one of the vaccine sites in a woman with advanced rectal cancer 7 months after injection. She had received no other treatment and had slowly advancing disease.

We are aware of no other complications of the vaccine itself. For a time an effort was made to use a preparation that was bacteriologically sterile. In the 40 patients given cellular suspension the tumor was handled aseptically. In those prepared with ulcerated tumor there was gross contamination, and yet they have had no untoward reactions and no infections.

DISCUSSION

Autogenous vaccines with Freund's adjuvant can be given to cancer patients without serious sequelae, in patients observed as long as almost 3 years. When this study started, there was grave concern for possible systemic effects of the vaccine, such as nephritis or neuritis. This experience is reassuring. Nothing was observed to suggest that the vaccine has contributed to the patient's death or progression of the disease.

It is our impression that some of the patients have been benefited by the vaccine. The 6 cases in which extensive tumor was

removed by a narrow margin and in which there are 5 patients clinically free of disease are suggestive.

The 2 cases in which gross disease was left after partial local excision and in which now there is no demonstrable tumor also suggest some possible benefit. This favorable course could conceivably result from sepsis or ischemic necrosis but neither of those factors seemed of significance here. It is of interest that both of these patients had squamous carcinoma. Several other patients, also, who were apparently benefited, had squamous carcinoma. We are aware of no benefit, even transiently, from chemotherapy in squamous lesions.

The vaccine appears to exert an effect potentiating radiotherapy. In 58 patients who subsequently were irradiated, 7 (12 per cent) are free of disease and 7 (12 per cent) have quiescent disease. Moreover, the cytologic picture in some patients undergoes a dramatic increase in SR and histiocytes (see Fig. 1). Cervical cancer associated with high SR and many histiocytes is much more sensitive to irradiation than those with poor SR and few histiocytes, e.g., the 5 year cure rate is 73 per cent and 15 per cent respectively. Actually, vaccine administration is the most effective means known of eliciting and increasing SR.

An unexpected feature of this study is the difficulty experienced in obtaining sufficient tumor for preparation of the vaccine. In only a minority is the cancer found in large enough masses to provide 5 grams of relatively pure tumor. Some patients with advanced, incurable disease had undergone a fruitless laparotomy. In others, grave technical difficulties were experienced in obtaining tumor without entering bowel or damaging the urinary tract. In 2 patients major sepsis developed in hematomas incident to operation for tumor antigen.

From this experience we conclude that autogenous vaccines exert an effect on patients and their tumors. A small but probably significant minority follow a more favorable course than expected. Some patients and tumors seem to become more sensitive to ionizing radiation under the influence of the vaccine.

SUMMARY

Vaccine prepared from the patient's own tumor and Freund's adjuvant was given to patients with advanced cancer. One hundred and one patients who lived more than 1 month after vaccination were observed for from 7 to 30 months. Fifty-five per cent lived 7 months or more and 14 per cent are living apparently free of disease. The vaccine may exert an effect that potentiates radiotherapy given after vaccine. There have been no serious systemic complications.

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EFFECTIVENESS OF TREATMENT OF SEVERE AMMONIA TOXICITY

WALTER LAWRENCE, JR., M.D., PARKER VANAMEE, M.D., J. WILLIAM POPPELL, M.D., and HENRY T. RANDALL, M.D., F.A.C.S., New York, New York

THERE are numerous observations, both clinical and experimental, that relate blood ammonia elevation to hepatic failure and hepatic coma. Controversy continues regarding the significance of the blood ammonia elevations as well as the value of various modes of therapy. Review of our experience with the treatment of hepatic coma associated with ammonia toxicity is the subject of this report.

The clinical physiology of blood ammonia has been extensively reviewed by the publications of McDermott, Najarian and associates, and many others. The major endogenous source of ammonia is the gastrointestinal tract where ingested nitrogenous substances in the presence of bacterial enzymes are a potent source of ammonia. Decomposition and absorption result in an increase in portal venous ammonia, but this is largely converted to urea by the liver. Under normal conditions the systemic circuit maintains a low blood ammonia level (less than 1 gamma ammonia nitrogen per c.c.).

The two major routes by which the peripheral blood ammonia may become elevated are shown diagrammatically in Figure 1. The first route is exemplified by any clinical situation in which the portal venous blood bypasses the liver. The other major means of blood ammonia elevation is the incomplete removal of ammonia from the portal blood that actually flows through the liver. Using this simple schema, the clinical settings for ammonia toxicity can be roughly grouped into two such categories.

From the Departments of Surgery and Medicine of Memorial Center, and the Andre and Bella Meyer Physiology Laboratories of the Sloan-Kettering Institute, New York.

Simple portal venous bypass of the liver is exemplified by those patients in whom surgical portacaval shunts are constructed for the treatment of portal hypertension or for resection of malignant neoplasms involving the portal vein. Inadequate removal of ammonia from portal blood by the liver is the mechanism affecting the patients in whom ammonia toxicity from extensive neoplastic replacement of the liver or severe hepatitis develops. A combination of these two mechanisms for ammonia elevation may exist in patients with portal cirrhosis. These patients have chronic liver damage as well as natural portal systemic shunts associated with portal hypertension. When ammonia toxicity due to ingested ammonium salts or gastrointestinal bleeding develops in such a patient the condition more closely resembles that of the clinical group in which large quantities of ammonia bypass the liver. When spontaneous ammonia toxicity due only to progression of the advanced intrahepatic process develops in a cirrhotic patient, the condition more closely resembles that of the clinical group in which primary hepatic failure is the causative factor. With this concept of the etiology of ammonia intoxication, we endeavored to study the results of treatment of patients within these various categories.

The therapy of mild ammonia toxicity consists primarily of the control of exogenous and endogenous sources of ammonia by means of oral restriction of such compounds, cleansing the colon with enemas, and use of intestinal antibiotics. When ammonia toxicity is associated with actual coma, additional measures are needed to

TABLE I.—RESULTS OF TREATMENT OF AMMONIA TOXICITY

	No. of patients	Clinical improvement		$NH_3 \downarrow$ >0.5 γ/c.c.		Survival	
		No.	Per cent	No.	Per cent	No.	Per cent
Portacaval shunt (surgical)	8	7	87.5	5/7	71.4	7	87.5
Portal cirrhosis with g.i. hemorrhage							
Precoma	5	4	80	—	—	2	40
Coma	17	12	70.5	—	—	6	35.3
All cases	22	16	72.7	11/12	91.6	8	36.4
Portal cirrhosis without g.i. hemorrhage							
Precoma	16	11	68.7	—	—	11	68.7
Coma	19	9	43.4	—	—	4	21.1
All cases	35	20	57.1	19/26	73.1	15	42.9
Hepatitis							
Precoma	2	2	100	—	—	1	50
Coma	4	2	50	—	—	2	50
All cases	6	4	66.7	2/5	40	3	50
Neoplastic infiltration of liver							
Precoma	12	9	75	—	—	1	8.3
Coma	17	7	41.6	—	—	2	11.7
All cases	29	16	55.2	18/24	75	3	10.3
All patients	100	63	63	59/74	79.7	46	46

reduce the elevations of blood ammonia and prevent irreversible central nervous system damage. Glutamic acid, as the monosodium salt, has been used clinically for this purpose in view of its "ammonia binding" capacity. Arginine hydrochloride has also been utilized clinically on the assumption that arginine, as it is a precursor of ornithine, would enhance urea synthesis in the liver.

According to these theories, glutamic acid does not require the presence of functioning liver to combine with ammonia whereas arginine is incapable of lowering blood ammonia without the presence of some hepatic function. The actual amount of functioning liver required to maintain urea synthesis is probably small enough, however, to make this differential between these amino acids of little clinical significance. A clinical study has been reported by Najarian, Harper, and McCorkle using arginine hydrochloride to combat ammonia accumulation. This report is presented in order to evaluate critically the effectiveness of the treatment of those patients having severe ammonia toxicity with the use of monosodium glutamate.

METHODS

For this evaluation, some selection of patients seemed necessary and we elected to include only those patients in whom significant clinical signs and symptoms of ammonia toxicity developed in association with definite elevation of blood ammonia. All patients exhibiting mild neurologic symptoms (or stage I as described by Najarian and associates) were eliminated from the study as these patients did not require aggressive amino acid therapy. Also rejected from this evaluation were those patients who had ammonia toxicity secondary to obvious exogenous sources of ammonia, as this problem can generally be treated effectively by simple elimination of the drug or compound. After this degree of selection, there remained for study 96 patients with 100 separate episodes of ammonia toxicity. All patients exhibited either stupor (precoma) or frank coma.

Treatment of this selected study group included the following measures: (1) correction of electrolyte abnormalities; (2) glucose infusions; (3) blood transfusion when necessary; and (4) administration of monosodium glutamate intravenously (usually 80

gm. over a 24 hour period). Potassium chloride (80 to 120 mEq.) was administered parenterally during the same period to counteract the metabolic alkalosis produced by such large dosage of monosodium glutamate.

Evaluation of therapy included the following features: (1) presence or absence of clinical improvement in mental status; (2) the effect on the blood ammonia level (Seligson modification of the Conway method); and, (3) survival or death of the patient with this specific episode of ammonia toxicity. These criteria of success or failure of the plan of therapy in each patient were correlated with the stage of coma as well as the clinical category of ammonia toxicity. These categories were as follows: surgical portal systemic shunt, 8 patients; portal cirrhosis with gastrointestinal hemorrhage, 22 patients; severe hepatitis, 6 patients; portal cirrhosis without gastrointestinal hemorrhage (spontaneous liver failure), 35 patients; and neoplastic replacement of the liver, 29 patients.

RESULTS

Biochemical abnormalities. The blood ammonia was consistently elevated in this entire study group because of the selection of patients as described. The range was 1.5 to 6.2 gammas per cubic centimeter.[1] The other major electrolyte abnormality frequently observed was respiratory alkalosis. There were adequate criteria to make this diagnosis in the immediate pretreatment period in 75 of the 100 episodes of ammonia toxicity. The presence of respiratory alkalosis was noted on occasion in the remaining 25 patients, but not in the immediate pretreatment period.

The effect of the degree of neurologic abnormality on the result of treatment. Sixty-five of these 100 episodes of severe ammonia intoxication were associated with frank coma in which the patient could be aroused only by deep stimuli, if at all. This would correspond

[1]Normal range with Seligson method in our laboratory is less than 1 gamma per cubic centimeter.

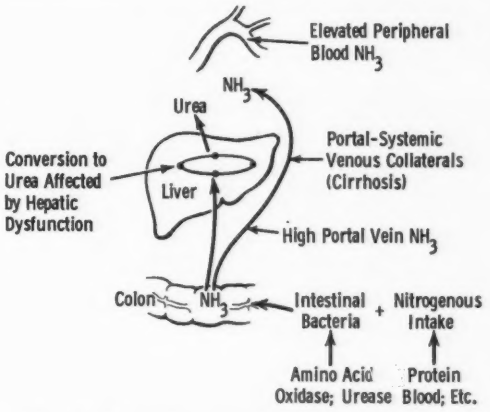

FIG. 1. Two major routes by which peripheral blood ammonia may become elevated.

to stage 3 of the schema proposed by Najarian, Harper, and McCorkle. Of this group, only 56.9 per cent were clinically improved by the therapy outlined and only 32.3 per cent survived the specific episode of hepatic coma under study. Of the 35 other patients exhibiting only stupor or precoma (stage 2), the results were slightly better. Of this group, 75.3 per cent were clinically improved by the treatment whereas 57.1 per cent survived the episode studied.

The effect of etiology of ammonia intoxication on the therapeutic result. Blood ammonia.—The 100 episodes of ammonia intoxication described were classified as outlined. The therapeutic program described resulted in a decrease in blood ammonia of 0.5 gamma per cubic centimeter (or more) in 79.7 per cent of the 74 patients in whom a second blood ammonia determination was possible. The frequency of such a decrease in blood ammonia in the various groups described is seen in Table I. It should be noted that patients with severe hepatitis were the only group in whom the blood ammonia was relatively unaffected by monosodium glutamate.

Clinical improvement. An improvement in mental status was observed in 63 of the 100 patients treated. Initial improvement in this regard was most frequent in patients with

TABLE II.—RESULTS OF TREATMENT OF AMMONIA TOXICITY AS TO SITE OF HEMORRHAGE IN CIRRHOTIC PATIENTS

	No. of patients	Clinical improvement		Total		NH_3 ↓ >0.5 γ/c.c.		Survival	
		Partial	Marked	No.	Per cent	No.	Per cent	No.	Per cent
Hemorrhage from esophageal varices....	15	9	2	11	73.7	8/9	88.9	5	33.3
Hemorrhage from other site in g.i. tract.....	7	1	4	5	71.4	3/3	100	3	42.9
All cirrhotic patients with hemorrhage	22	10	6	16	72.7	11/12	91.6	8	36.4

surgical portal systemic shunt (87.5 per cent). Ammonia intoxication following gastrointestinal bleeding in the presence of cirrhosis was definitely improved in 72.7 per cent of patients. Therapeutic effectiveness was definitely less in patients with hepatitis, spontaneous hepatic coma with cirrhosis, and patients with primary or metastatic cancer in the liver. The results are graphically demonstrated in Table I and Figure 2.

Effect of treatment on survival. A smaller number of patients survived the episode of ammonia toxicity than demonstrated initial clinical improvement from therapy. There were only 46 patients of this series of 100 episodes of ammonia intoxication who survived the episode in question, despite the fact that treatment was sometimes repeated on several occasions. All but 1 of the 8 patients with ammonia toxicity following portal systemic shunt survived after the therapy outlined. Three of the 6 patients with severe hepatitis survived and each of these patients received massive cortisone administration in addition to the therapy for blood ammonia elevation. Of the patients with portal cirrhosis in whom spontaneous ammonia toxicity developed, 42.9 per cent survived following treatment, despite the fact that initial improvement was not as frequent as in those patients with cirrhosis in whom ammonia intoxication developed after gastrointestinal hemorrhage. Survival in this bleeding group was low (36.4 per cent), but it should be noted that 11 of the 14 deaths occurring in this group were associated with inadequate control of the hemorrhage. The site of bleeding (esophageal varices or elsewhere) had little effect on survival rate or the other factors studied (Table II). The most striking observation in regard to survival was the fact that only 3 of 29 patients with neoplastic infiltration of the liver (10.3 per cent) survived the specific episode of ammonia intoxication, although death was delayed for from 1 to 2 weeks in 6 additional patients (Fig. 2).

DISCUSSION

The treatment of ammonia intoxication, when it can be attributed to exogenous administration of ammonia containing compounds, is relatively effective. This is also true when the symptomatology is mild. For this reason, all patients who did not satisfy the criteria described were not included in this analysis. This strict selection undoubtedly has some bearing on the low rate of clinical improvement and immediate survival observed. The importance of the degree of neurologic abnormality is also emphasized by the more satisfactory therapeutic response when the clinical problem was precoma rather than advanced coma. The type of case selection utilized in this study makes comparison of therapy by monosodium glutamate with other methods somewhat difficult. This study does make possible, however, an evaluation of clinical

improvement and survival in relation to significant decrease in blood ammonia in patients who seem to require aggressive treatment. The addition of other supportive therapy made a pure evaluation of the role of amino acid therapy impossible. The serious nature of this clinical problem necessitated the use of such a combined therapeutic plan. It was most striking, however, that despite an effective decrease in blood ammonia in many instances, the therapeutic result was often unsatisfactory.

The correlation of the effectiveness of therapy with the various types of clinical situations in which ammonia toxicity was found was of interest. The patients with portal systemic shunts in whom postoperative ammonia toxicity developed and the cirrhotic patients in whom ammonia toxicity developed following massive gastrointestinal bleeding might seem to fit the etiologic category described as "portal venous bypass of the liver." Although a number of the patients with gastrointestinal bleeding did not survive because of continued and uncontrolled hemorrhage, these two groups had the most pronounced clinical improvement immediately following therapy. On the other hand, patients with cirrhosis of the liver in whom spontaneous ammonia toxicity developed, and those in whom this syndrome developed on the basis of replacement of the liver by cancer were improved to a lesser extent, as were those patients with severe hepatitis. Primary hepatic dysfunction played the larger role in the etiology of ammonia intoxication in these last three clinical groups.

One of the disturbing features of the concept of clinical ammonia toxicity has always been the incomplete correlation between the severity of the neurologic abnormalities and the degree of blood ammonia elevation observed. This has been partially explained by comparative study of arterial and venous levels of ammonia, measurement of cerebrospinal fluid ammonia, studies of the effect of blood hydrogen ion concentration on blood ammonia levels, and theoretic considerations of the relative proportion of free ammonia (PNH_3) and ammonium ion. The high incidence of respiratory alkalosis in patients with clinical ammonia toxicity is important in that this disturbance also affects function of the central nervous system. Although each of these factors undoubtedly plays some role in the difficulty of correlation, the degree of disturbance of other hepatic metabolic functions that may affect the central nervous system undoubtedly contributes to this continuing confusion.

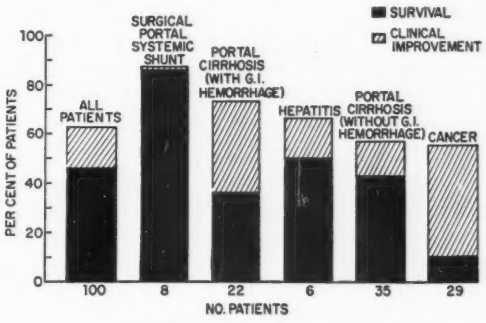

FIG. 2. Results of therapy of hepatic coma.

The incomplete clinical correlation with blood ammonia levels is further confused by our clinical impression that adaptation to minor elevation of blood ammonia seems to occur in some patients with long-standing liver disease. Acute elevations in blood ammonia of similar magnitude in the clinical setting of normal liver function seem poorly tolerated. An example of this phenomenon is the severe problem that ensues when a portal systemic shunt is carried out because of resection of the portal vein for carcinoma of the pancreas or distal portion of the stomach. This observation is further supported by laboratory observations. Dogs subjected to immediate Eck fistula have much more difficulty with ammonia toxicity than those animals in whom preliminary staged ligation of the portal vein is performed prior to a similar operation as Bollman and associates have shown. An analogy might be drawn between the clinical categories described, therapeutic results

of treatment, and the two types of ammonia intoxication observed in the experimental laboratory. The more favorable group of patients is exemplified by the Eck fistula dog, which can be effectively treated in most instances when experimental "meat intoxication" syndrome is produced. The patients with primary hepatic dysfunction are more similar to the dogs subjected to total hepatectomy. This experimental preparation develops a progressive elevation of blood ammonia which we have effectively lowered by monosodium glutamate, but the dehepatized animal seems in no way clinically improved by such therapy (2).

It would appear from these clinical and experimental observations that ammonia must be an important factor in the pathogenesis of hepatic coma, but is probably not the only factor contributing to the critical state in most patients exhibiting this syndrome. The relative importance of the elevation in blood ammonia is probably related to the proportional roles played by portal venous bypass and hepatic dysfunction. A therapeutic program involving amino acid therapy is apparently more effective when this ammonia elevation is the result of portal venous bypass and seems of less benefit when the primary problem is advanced disease of the hepatic parenchyma. When clinical improvement does occur in this primary hepatic dysfunction group, it may be related to the ability of the liver to restore some function, rather than any effect on the blood ammonia itself. This capacity for functional improvement may account for the higher proportion of satisfactory responses in patients with either hepatitis or cirrhotic decompensation than with those patients who had enough infiltration with neoplasm to produce ammonia toxicity.

Arginine hydrochloride has been said to be more effective than monosodium glutamate in the treatment of hepatic coma due to ammonia intoxication. We have not found this to be the case from our limited experience with the use of this amino acid. However, the statistical results of therapy of hepatic coma with glutamate reported herein are less favorable than those reported with arginine hydrochloride. This may well be explained by the fact that ammonia intoxication developed on the basis of primary hepatic dysfunction in a higher proportion of patients in this series. In addition, all mild forms of ammonia toxicity were eliminated from this study.

SUMMARY

The therapy of 96 patients with 100 episodes of severe ammonia toxicity (precoma and coma) has been evaluated. The treatment plan combined supportive therapy with intravenous monosodium glutamate. The results for the entire group were tabulated in terms of decrease in blood ammonia (79.7 per cent), clinical improvement in mental status (63 per cent), and immediate survival (46 per cent). The etiology of the ammonia toxicity was correlated with these criteria of therapeutic effectiveness. The findings suggest that ammonia toxicity secondary to circulatory bypass of the liver was more easily managed than those clinical situations in which the elevation in blood ammonia was secondary to hepatic dysfunction. Treatment of the elevation in blood ammonia in patients with advanced hepatic failure and coma appeared to be helpful; however, the results were far from ideal.

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MANAGEMENT OF SUPRACONDYLAR FRACTURES OF THE HUMERUS IN CHILDREN

JOHN J. GARTLAND, M.D., F.A.C.S., Philadelphia, Pennsylvania

FEMORAL NECK FRACTURE has been termed the "unsolved fracture." In a similar vein, supracondylar fracture of the humerus in children might be called the "misunderstood fracture." By common consent, this is the most frequent fracture seen about the elbow in children. Blount states the incidence is 60 per cent. At the Fitzgerald-Mercy Hospital the incidence was 50 per cent from 1953 through 1957. In spite of its incidence, however, cases of severe residual bony deformity and dreaded Volkmann's contracture continue to be seen. In a recent article in the French literature, Fevre and Judet discuss in some detail their results in the operative treatment of 17 cases of established Volkmann's contracture. In 10 of these 17 cases, the initial trauma was a supracondylar fracture of the humerus.

Although methods of management for this injury are well documented, it is interesting to observe the trepidation with which men, otherwise versed in the management of trauma, approach a fresh supracondylar fracture. In many instances, their trepidation is justified because of the tragic complications that might ensue from this injury and the radical modifications in routine treatment that might be involved to prevent permanent functional loss, permanent cosmetic deformity, or damage to the overlying neurovascular structures. In his earlier years, the surgeon's confidence in his method of management is not strengthened by the fact that the opinions of authorities differ regarding reduction, immobilization, and after care. No problem should exist in the larger teaching centers where all types of skilled help and advice are available. However, a large proportion of these cases are seen in suburban and rural hospitals where, in the main, trained help is minimal.

From the Fitzgerald-Mercy Hospital, Darby, Pennsylvania.

Since cases of residual bony deformity and Volkmann's contracture continue to be seen, it is evident that the simple basic principles underlying the management of this fracture are still not universally understood by all those called upon to treat this injury. If one becomes responsible for the treatment of these cases, methods of management must be adopted that prove practical and successful from both the patient's and the doctor's standpoint.

This article is presented to re-emphasize the principles underlying the treatment of this common injury and to discuss a method of management which has proved practical and successful for any situation, and especially for hospitals where trained constant orthopedic supervision is not available, and where much of the immediate after care is supervised by personnel not yet fully trained in the management of fracture cases.

TYPES OF FRACTURE

By definition the fracture line in this injury crosses the supracondylar area of the distal humerus, just proximal to the articular surface of the elbow joint. The fracture line may be transverse and jagged, or, less commonly, it may run obliquely upward and backward, beginning on the anterior surface of the humerus just proximal to the distal articular surface. This results in a small distal fragment composed of the lower articulating end of the humerus but to which is attached the elbow joint and forearm, and a larger proximal fragment which is the anteriorly spiked humeral shaft.

In the vast majority of cases, the distal fragment is displaced posteriorly but may, rarely, be displaced anteriorly depending on the direction of the fracturing force. The direction of the fracture line usually has an important bearing on treatment. As a rule, the fragments separated by a transverse fracture line are more easily reduced and held. Those separated by a long oblique fracture line are frequently more difficult to reduce and often slip during the postreduction period. The small distal fragment is most often intact but may be comminuted with extension into the lateral condyle, and medial condyle, or through one of the epiphyseal plates.

It is important to remember that the distal fragment is usually also rotated on the proximal fragment, more frequently internally. There are, therefore, two positional deformities to be corrected at reduction. If the rotary displacement is not corrected, it results in permanent abnormality of the carrying angle. Inadequate reduction of the posterior displacement results in limitation of flexion or extension.

It serves no useful purpose to subdivide these fractures further into dicondylar or transcondylar types. They are all fractures of the supracondylar area of the humerus, varying only in the degree of displacement and comminution. Normally, the distal articular surface of the humerus tilts forward at an angle of approximately 30 degrees with the shaft. The pathologic anatomy of this fracture, therefore, results in a loss of this angle plus a rotational spin of the distal fragment. Three types of supracondylar fractures are seen clinically. One is the nondisplaced type, second is the minimal to moderately displaced type, and thirdly, the severely displaced fracture (Figs. 1, 2, and 3). The only question, then, that should concern the surgeon is what method of treatment will give the best result in each type.

TREATMENT

Successful treatment of this injury involves adequate reduction and adequate immobilization. It is well to remember that the typical patient is an otherwise healthy active child, and the immobilizing apparatus will soon be called upon to withstand the stresses and strains of childhood. To be truly successful, treatment methods should be simple so that they can give consistent results in the smaller hospitals where trained orthopedic help is minimal.

Every child with a suspected elbow fracture should have an x-ray examination of both elbows. Immediate check should be made to determine the presence or absence of circulatory embarrassment or nerve damage. Treatment should be undertaken as soon as the diagnosis is established. This is one injury that brooks no delay. Swelling about the elbow enlarges with delay and increases the incidence of complication, both bony and vascular.

Fracture with no displacement. In these cases the fracture line is almost always transverse, and there is no posterior displacement of the distal fragment and no rotational deformity. The angle of the forward tilt of the distal articulating surface of the humerus may be normal, or may be decreased down as far as zero degrees. There will be generalized swelling about the elbow joint, sometimes moderately severe. As a rule, there will be no evidence of nerve or vascular complication.

In the presence of negligible or no displacement, no actual reduction is necessary. The injured arm is immobilized in a padded posterior plaster splint extending from the metacarpal heads, with the forearm in neutral rotation, to a comfortable height beneath the axilla. The forearm is flexed to 75 or 80 degrees. The position of acute flexion is unnecessary and only further compresses an already swollen elbow. The plaster splint is held in place by circular gauze bandage loosely applied so there are no tight edges cutting across the front of the flexed elbow. The status of the pulse is again checked after application of the splint.

The child is re-examined within a 24 hour period with special attention to elbow swell-

FIG. 1. Roentgenogram showing minimal to no displacement.

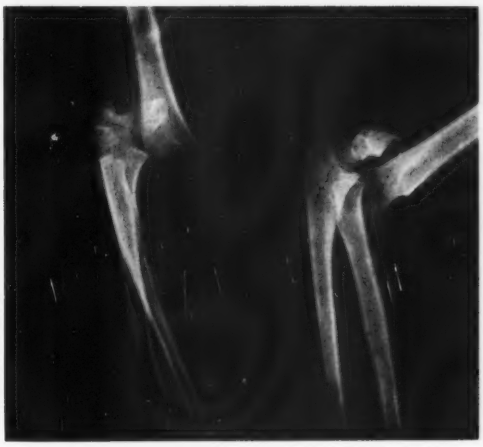


FIG. 2. Roentgenogram in this instance shows moderate displacement.

ing, radial pulse, finger sensation, and pain. After 1 week, the plaster splint is removed and a long-arm circular cast is applied with the elbow in the same degree of flexion. The long arm cast is removed after a further period of 3 weeks and a roentgenogram is taken. If healing is adequate, as it usually is in this type of fracture at 4 weeks, active motion and hot soaks are started. No formal physical therapy treatments are used or needed. No passive stretching either by a second person or by the carrying of weights is ever indicated. Full functional return without deformity can be expected.

Fracture with moderate displacement. All children with moderately displaced supracondylar fractures should be admitted to the hospital for at least a 48 hour period because these fractures require a gentle closed manipulative reduction under a general anesthetic to realign the posteriorly displaced and rotated small distal fragment accurately. The incidence of vascular and nerve complication increases with displacement and swelling, making careful observation of the patient mandatory.

In the great majority of cases of moderate displacement, accurate reduction of the posterior displacement and rotational deformity can be obtained by gentle closed manipulation (Fig. 4). Immobilization is again secured by means of a padded posterior plaster splint, as is used on the nondisplaced fractures, with the elbow flexed to 75 or 80 degrees, and the forearm in neutral rotation. The rule of thumb usually given to determine the amount of flexion for the immobilized elbow is to flex the elbow to the point where the radial pulse weakens, then extend it 10 to 15 degrees. In the vast majority of cases, the final position of elbow flexion lies between 75 and 80 degrees.

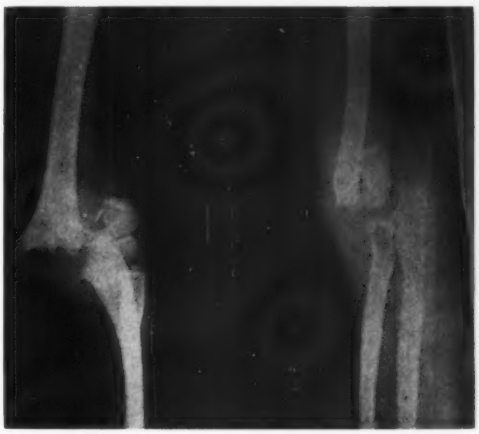


FIG. 3. Roentgenogram in this instance shows severe displacement.

a

b

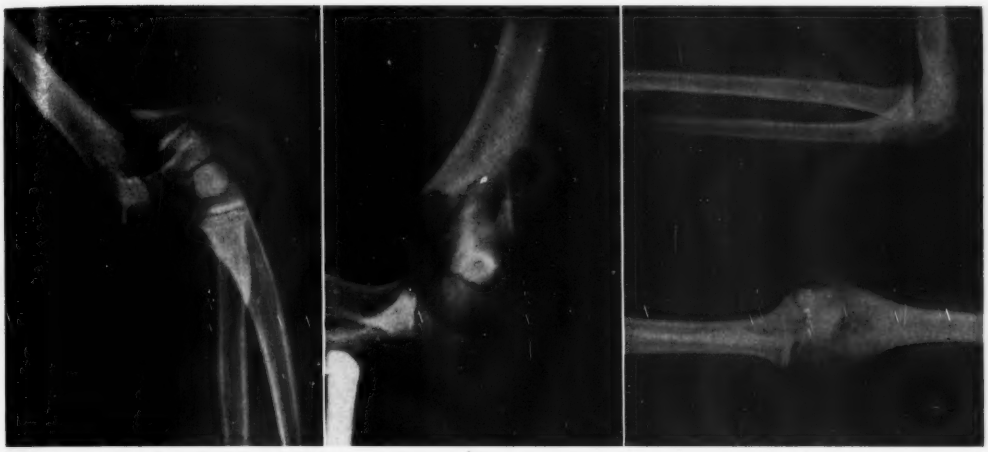
FIG. 4. a, Roentgenogram of fracture with moderate displacement. Prereduction view. b, Lateral view which was taken after manipulative closed reduction.

The volume of the pulse is again noted as soon as the splint is applied. The status of the reduction is checked by x-ray examination as soon as possible, and careful watch is kept on the patient as regards circulation, finger sensation, and amount of forearm pain with finger motion. The posterior splint is removed at the end of 1 week, and a long-arm circular cast applied with the elbow in the same degree of flexion and the forearm in neutral rotation. The long arm cast is removed after a further period of 5 weeks, and the status of the healing checked by x-ray examination. Gradual active motion and hot soaks can then be started.

Occasionally, a moderately displaced fracture will be seen that proves to be unstable, and the reduction cannot be maintained by the plaster methods described. These are almost always oblique fractures and require overhead skeletal traction, as described in the next section, to insure accurate reduction and immobilization. The skeletal traction is maintained for 2 to 3 weeks. A long-arm plaster cast is then applied for a further period of 3 to 4 weeks.

Fracture with severe displacement. Some fractures with severe displacement, especially if the fracture line is transverse, and if the distal fragment is not comminuted, reduce readily with closed manipulation, and prove stable in the postreduction period. These are handled by the plaster method already described. A greater number of severely displaced fractures occur in which the fracture line is oblique. These are unstable fractures and the reduction cannot be maintained by plaster immobilization. These fractures require overhead skeletal traction as their primary definitive treatment.

Properly, skeletal traction in these cases should be set up in the operating room under the usual operating room conditions, and using general anesthesia. A threaded Kirschner wire of adequate gauge is used. The wire is inserted with a hand drill through



a b c

FIG. 5. a, Comminuted supracondylar fracture. a, Olecranon skeletal traction elected as primary definitive treatment. b, Lateral view of same elbow after 2 weeks in skeletal traction. This position accepted. c, Same elbow 5 years later. Complete range of motion. No cosmetic deformity other than being palpably thicker than opposite elbow.

both cortices of the prominent border of the ulna, about 1½ inches distal to the olecranon tip. It is better to insert the wire from the medial aspect to avoid damage to the ulnar nerve. A yoke is attached to the wire and the wire ends are corked. The yoke is then attached to the rope and pulley system, and traction is instituted with the arm suspended over the patient's chest, with the elbow flexed to 90 degrees. A volar plaster splint is bandaged to the forearm and wrist to prevent the wrist and hand from hanging in a "wrist-drop" position. The forearm is suspended in a wide sling. Enough weight is added to the traction just to hold the shoulder slightly off the bed.

The status of the fragments should be rechecked by x-ray examination within 24 hours. If reduction is complete and satisfactory, traction is maintained for a 2 to 3 week period as the immobilizing agent. At the end of this time, traction is discontinued and the wire removed. A long-arm plaster cast is applied immediately with the forearm in neutral rotation, and the elbow is flexed to 90 degrees. Immobilization is continued for a total period of 6 weeks (Fig. 5). If the recheck roentgenogram reveals unsatisfactory reduction, the solution is not to increase the amount of traction. It is better to manipulate the fragments manually into place under a second anesthesia without disturbing the traction force, and to continue the traction as the immobilizing agent. If necessary, even another manipulation could be carried out after several days, if the position is not acceptable. Once an acceptable reduction has been obtained, the traction is maintained for 2 to 3 weeks, followed by a long-arm cast for a total immobilization period of 6 weeks (Fig. 6).

In all cases in which the distal fragment is comminuted and in most compound fractures, overhead skeletal traction is the treatment of choice. In most compound cases, it is usually the sharp spike on the anteriorly displaced proximal humeral fragment that perforates the volar skin surface. It follows, therefore, that in this situation the fracture line will be oblique and the distal fragment will be severely displaced. After debridement of the wound, primary skeletal traction insures good reduction and adequate immobilization, and allows the wound to be observed and dressed without compromising the reduction.

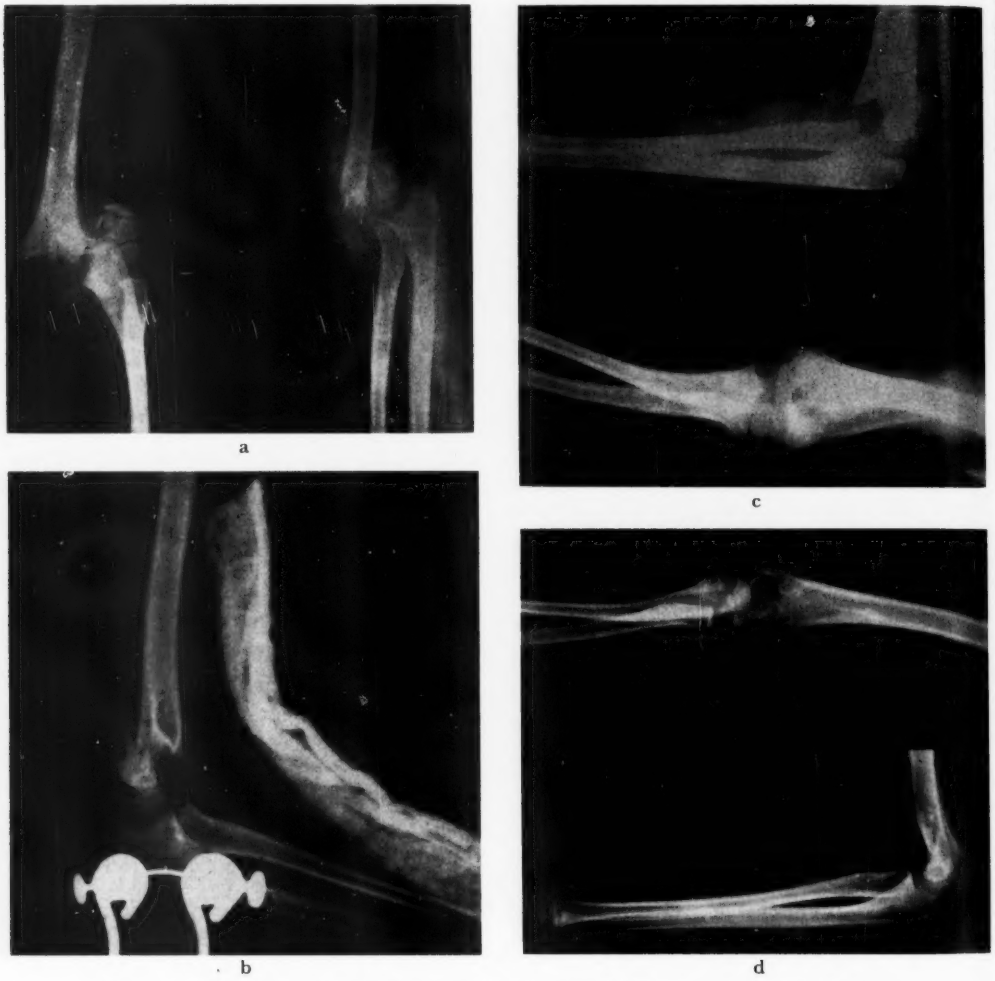


FIG. 6. a, Prereduction film showing severe displacement. b, Closed manipulative reduction unsuccessful and olecranon skeletal traction instituted. This is first check x-ray film after start of skeletal traction. Present position not acceptable. c, This patient had 1 closed manipulative reduction and 2 further manipulations under anesthesia after skeletal traction instituted. This is position when cast was removed at 6 weeks. d, X-ray appearance 4 years later. Range of motion and physical appearance completely normal.

COMPLICATIONS AND THEIR MANAGEMENT

The complications of a supracondylar fracture arise because of: (1) inadequate reduction, (2) circulatory impairment, heralded by a weak or absent radial pulse, and (3) rarely, damage to the nerves passing over the fracture site.

Inadequate reduction. After closed reduction has been performed, a postreduction roentgenogram may show a partial reduction of a posteriorly displaced distal fragment, persistent overriding of the fragments, or a residual lateral or medial displacement.

Partial reduction of a posteriorly displaced distal fragment is acceptable provided the angle of the distal articular sur-

face of the humerus measures, at least, zero degrees with the shaft. Persistent posterior displacement is not acceptable. Angular deformity, at this site, does not correct with growth, and results in permanent limitation of flexion.

Persistent overriding is never acceptable. If not too great, it sometimes corrects with subsequent growth, but most often results in limited elbow function. Persistent overriding, therefore, justifies further attempts at reduction. If a second manipulation is not successful, overhead skeletal traction should be instituted and the fracture managed as those with severe displacement. Open reduction with or without metal fixation is not believed to be indicated in the treatment of a displaced closed supracondylar fracture.

Residual lateral or medial displacement, or rotation of any significance, is not acceptable and justifies remanipulation. Allowing this deformity to remain, even in the face of accurate reduction of the posterior displacement, will lead to a permanent alteration in the carrying angle with either a cubitus valgus or cubitus varus deformity. Residual rotation of the distal fragment is frequently difficult to detect clinically, especially when palpation is through a swollen indurated elbow area. Its presence can be determined if 3 x-ray views are obtained: (1) a true anteroposterior view of the arm with the shoulder and elbow joints visible on the film, (2) a true lateral view of the elbow joint, and (3) a Jones view, or an anteroposterior view through the flexed elbow (Fig. 7). If this type of displacement cannot be maintained in reduction because of instability at the fracture line, overhead skeletal traction should be instituted.

Circulatory impairment. The most dreaded complication of a supracondylar fracture is an extremely weak or absent radial pulse. This may be present before reduction, or may appear after the reduction, and may have several causes. An absent radial pulse may be due to direct impingement of the neurovascular structures on the distal sharp end of the anteriorly displaced proximal fragment, or may be due to compression of the vessels at the elbow secondary to severe swelling, or, rarely, may be because of a lacerated or torn brachial artery.

FIG. 7. Jones' view of freshly reduced displaced supracondylar fracture.

Cases have been reported in which the radial pulse has remained absent, but the fingers maintained good capillary blood flow because of adequate collateral circulation. This is a fortunate circumstance but should not be depended upon. An absent radial pulse in the presence of a supracondylar fracture demands maximum effort as to its cause and correction. If ignored or uncorrected within a 6 to 8 hour period, Volkmann's ischemic contracture may result. In these cases mechanical occlusion of the venous circulation with ischemia and edema at the elbow, accompanied by vasospasm of the arterial tree, results in subsequent fibrosis of the volar musculature of the forearm and hand with severe crippling. This complication is entirely preventable.

When faced with an absent radial pulse

in a fresh supracondylar fracture, first thought should be given to reducing the fracture. The neurovascular structures are intimately bound to the distal fragment. Posterior displacement of the distal fragment causes the bundle to impinge on the distal sharp end of the anteriorly displaced proximal fragment. Therefore, if direct bone impingement is the cause of the absent radial pulse, the surest way of relieving compression of the brachial vessels is to reduce the fragments. Following reduction, the radial pulse should again be strong. The fracture is then immobilized in the indicated manner.

Several situations in regard to the radial pulse may present themselves. If direct bone impingement is the cause of the absent radial pulse, adequate reduction should restore the pulse. If the reduction is not adequate, further attention should be given to the fracture with either a remanipulation or the institution of overhead skeletal traction. If the reduction is adequate and the pulse remains precarious, search should be made immediately for another cause.

The most common cause of circulatory impairment is antecubital edema with subfascial tension and arterial vasopasm. In such a case, on first appearance the pulse may be adequate, but, after reduction, it may disappear with any attempt to flex the elbow, even to a right angle. As described in earlier communications (3, 5), the mixture of hyaluronidase and procaine offers an effective nonoperative method to relieve subfascial tension caused by edema and hemorrhage with great rapidity. The hyaluronidase rapidly disperses the offending fluid collection, and the procaine, which under the influence of the enzyme diffuses through a much wider area, relaxes any degree of arterial spasm present. Fifteen hundred turbidity reducing units of hyaluronidase mixed in 3 to 5 cubic centimeters of 1 per cent procaine injected into and about the antecubital fossa and into the fracture site will suffice to soften the elbow and restore the pulse in about 30 minutes, if this is the cause of the circulatory impairment. The fragments are then immobilized by either plaster or overhead skeletal traction, depending on the type of fracture.

One may be faced with a situation in which a radial pulse, absent before reduction, continues absent following reduction. The first step would be immediately to check the position of the fragments by x-ray examination. If the reduction proves satisfactory, the next measure would be the local injection of hyaluronidase and procaine as previously described. If the results from this are not completely satisfactory, it should be combined with a stellate ganglion block. If these measures are carried out correctly, the outcome will be satisfactory and surgical fascial release, specifically to relieve subfascial edema, will be unnecessary. Attention must also be given concurrently to maintaining the reduced fracture by either plaster fixation or overhead skeletal traction.

If all these measures prove unsuccessful, one is probably dealing with a torn or lacerated brachial artery. At this point, immediate exploration of the artery is indicated, with either repair or grafting in mind. Preliminary arteriography is believed to be an unnecessary hazard and is not recommended.

Nerve damage. Primary damage to the nerves passing over the elbow joint is uncommon with a supracondylar fracture. Stretching or contusion injuries to the median and ulnar nerves have been reported, but are rare. Occasionally, injury to the deep muscular branch of the radial nerve is noted.

The nerve damage in almost all cases is temporary and disappears in time without any specific treatment. It is important to pick up any evidence of nerve damage, if present, before the fracture is reduced. Its presence, however, does not modify the treatment except to see that further trauma is not given to the injured nerve. Definitive fracture care should be carried out just as if no nerve damage was present.

AFTER CARE

When the surgeon views the postreduction films, it is well to bear in mind what constitutes an acceptable reduction. The aim of treatment is to restore the normal anterior angulation of the distal articular surface of the humerus, plus the reduction of any medial or lateral displacement or rotation of the distal fragment. Partial reduction of a posteriorly displaced distal fragment is acceptable provided the angle of the distal articular surface of the humerus measures at least 0 degrees with the shaft. Mild residual overhang of the anterior surface of the proximal humeral fragment will resorb with growth and will not cause a flexion block. Acceptance of a negative angle at the distal articular surface of the humerus guarantees a flexion block because angular deformities are not improved by subsequent bone growth. Persistent posterior displacement, persistent overriding, persistent medial or lateral displacement, and residual rotation are not acceptable.

The duration of immobilization will vary from 4 to 6 weeks. In cases not requiring reduction, healing will be sufficient at the end of 4 weeks to start unprotected active motion. In cases in which manipulative reduction or skeletal traction is required, immobilization can usually be removed after 6 weeks. If it is planned to immobilize a supracondylar fracture for 6 weeks, it is wise to recheck position by x-ray examination at 3 weeks. A study of Colles' fractures (4) showed a surprising amount of the reduction to be lost while the wrist was in the cast. If the cast is loose at the time of the 3 week check, it should be replaced. If this film shows loss of reduction, it is quite possible to regain it at this time. It is impossible at 6 weeks.

Formal physical therapy is not required in these cases. Forceful passive stretching and the carrying of weights should be expressly forbidden. Children possess their own special brand of magic and will regain full function if left to their own devices and if the surgeon has done his part.

Myositis ossificans is rarely seen as a complication of a supracondylar fracture. It is quite frequently seen as a complication of posterior dislocation of the elbow, particularly if associated with fracture of the radial head. The reason for this can be seen in the anatomy of the area. The anterior elbow capsule is thin and loosely attached to the humerus. The brachialis anticus muscle overlies the anterior joint capsule and is attached to it. Anterior dislocation of the distal humerus at the elbow tears through the anterior capsule and brachialis muscle and the subsequent hemorrhage into the fibers of the brachialis muscle organizes and becomes ossified. In most supracondylar fractures, the anterior joint capsule remains intact and the hemorrhage is dissipated throughout the area because an escape route exists between the fragments. If myositis ossificans should complicate a supracondylar fracture, it frequently disappears if the immobilization is prolonged another 6 to 8 weeks. If it should not regress, operative removal of the anterior bone block should be postponed for 1 year. Early surgical intervention results in the formation of more bone.

Occasionally, residual bony deformity is seen as a complication in the follow-up period and results either in impairment of function or cosmetic deformity. With but 1 exception, this complication means the original reduction was inadequate. Subsequent growth over a long period of time may frequently correct a flexion block due to residual overriding, but it does not lessen a residual angular deformity, and never corrects residual rotation or displacement. Incomplete reduction of the posterior displacement results in limitation of flexion, and, if severe, requires an angular osteotomy of the distal humerus to restore an anterior angle. Incomplete reduction of medial or lateral displacement or rotation results in a cosmetic deformity due to cubitus valgus or cubitus varus. These are rarely associated with functional impairment. Correction of the carrying angle deformity requires a

rotational osteotomy of the distal humerus. The 1 exception occurs when the original fracture line injures the epiphyseal line at the distal humerus and the slow development of a carrying angle deformity in the late follow-up period becomes evident secondary to unequal bone growth. Here the deformity is cosmetic and will require a rotational osteotomy.

Tardy ulnar neuritis may be seen as a late complication in cases of supracondylar fracture. Its development is almost always secondary to a residual cubitus valgus deformity and requires an anterior transposition of the ulnar nerve for its treatment. Rarely, a symptomatic neuroma may form in the ulnar nerve because of irritation from the olecranon wire in cases in which overhead skeletal traction had been used.

The prognosis in supracondylar fracture should be excellent in regard to function and cosmetic alignment. Almost all the cases not classed as good or excellent are the result of inadequate reduction or improper management of complications. Except for problems arising from compounding, actual laceration or contusion of the neurovascular structures, or epiphyseal damage, all complications of supracondylar fractures are believed to be preventable.

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SURGICAL MANAGEMENT OF RAPIDLY EXPANDING INTRATHORACIC PULSATING HEMATOMAS

HARRIS B SHUMACKER, JR., M.D., F.A.C.S., and HAROLD KING, M.D., F.A.C.S.,
Indianapolis, Indiana

PULSATING HEMATOMAS of the thoracic aorta either tend to rupture early with fatal exsanguination or to develop into well organized chronic aneurysms with the passage of time. Gerbode and his associates have recently reviewed the surgical management of thoracic aortic aneurysms resulting from trauma. Eiseman and Rainer have dealt with this problem too and have also discussed the immediate management of thoracic aortic lacerations. Little is found in the literature concerning the emergency treatment of rapidly expanding intrathoracic pulsating hematomas. Murdock attempted to treat such a case but death occurred on the operating table. His patient, admitted to the hospital 2 hours after an automobile injury with x-ray evidence of a widened mediastinal shadow and partial right pneumothorax, was treated with apparent success during the first 9 days by multiple transfusions and by closed intercostal tube drainage and thoracenteses for bilateral hemothorax when this complication became evident. Suddenly, on the tenth day, severe pain, dyspnea, and marked widening of the mediastinal shadow on x-ray study developed. Thoracotomy was immediately carried out, but fatal hemorrhage occurred during the effort to isolate the aorta proximal and distal to large mediastinal pulsating hematoma. This resulted from a through-and-through tear of the aorta at eighth thoracic level.

Because of the paucity of information in the literature, it has seemed desirable to report our experiences with 3 emergency operations for rapidly expanding intrathoracic pulsating hematomas and to present certain concepts of management gained from these experiences. Two operations were carried out in 1 patient whose aneurysms were mycotic in origin. One was performed in a case of trauma.

From the Department of Surgery, Indiana University Medical Center, Indianapolis.

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CASE REPORTS

CASE 1. The patient was a 15 year old boy who was well except for difficulty in attaining normal weight until early June 1957 when he began to have high spiking fever and chills. Finding a blood smear suggestive of malarial parasites, his physician placed him on quinine and atabrine therapy. For a short while he seemed somewhat better and had less fever and chills. The high fever and chills returned, however, and were accompanied by anorexia. Achromycin was given for a short while without benefit. Pain developed in the left side of the chest, and a hacking, nonproductive cough as well. On admission to another hospital the diagnosis of patent ductus arteriosus, coarctation of the aorta, aneurysm of the aorta, and septicemia was made. On the night of July 5 he was transferred here.

On admission the patient was found to be a thin, critically ill patient with a marked yellowish atabrine discoloration of the skin and sclera. He was breathing with some distress on oxygen therapy. His temperature was 103.8 degrees, pulse 140, and respirations 28. Pulses were bounding in the arteries of the neck and upper extremities. The abnormal aortic pulse could not be felt and there were no pulses palpable in the lower extremities. The brachial blood pressure was 150/92. Precordial activity was greater than normal. A thrill could be felt over the pulmonic area. There was a harsh systolic and a brief diastolic murmur in this area. Posteriorly a continuous murmur could be heard. Breath sounds were good bilaterally. Roentgenograms brought with the patient and made on July 3 showed rib notching and a mass suggesting a moderate sized aneurysm (Fig. 1a and b). Blood was drawn for culture immediately and on 3 subsequent occasions during the remainder of the night. The diagnosis made was coarctation of the aorta associated

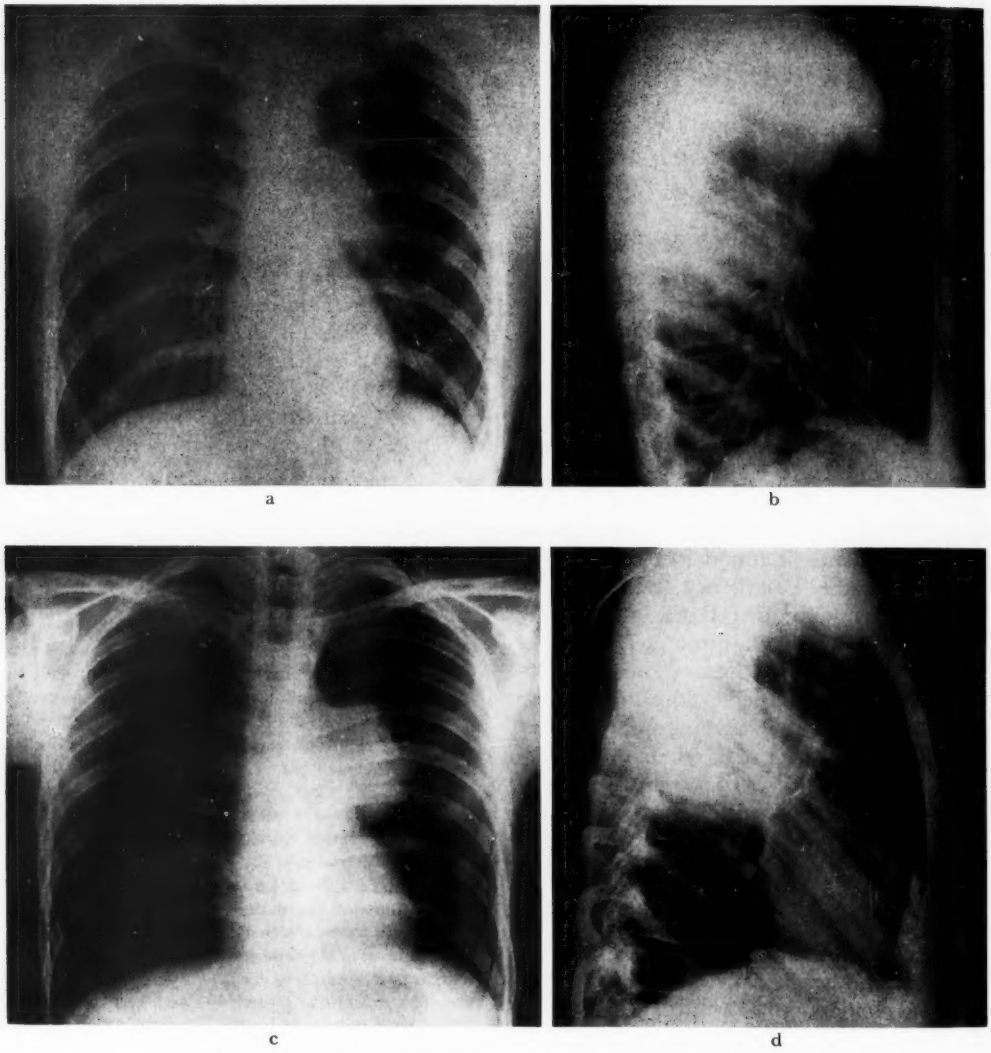

FIG. 1. Roentgenograms of the chest in Case 1 made on July 3 (a and b) and on July 6 (c and d). The increase in size of the hematoma on the later films is evident.

with patent ductus arteriosus, aneurysm, and septicemia. It was not known whether the aneurysm was an old one which had developed distally to the coarctation or whether it was of mycotic origin. The following morning fluoroscopic and x-ray studies were carried out. The mass was found to be much larger than it had been on the roentgenogram made 48 hours previously (Fig. 1c and d). The patient had now lost all breath sounds over the left hemithorax and it was thought he had left main bronchial obstruction with trapped air. A few hours earlier at the time of admission it had been hoped that time would allow intensive antibiotic treatment and later elective operation. However, the deterioration of the patient, the evidence of rapid expansion of the aneurysm, and the loss of breath sounds on the left side made immediate surgery mandatory. It was realized that the risk was great.

A long posterolateral incision was made and the chest was entered through the left fourth interspace. As soon as the chest was opened it was obvious that the impression of trapped air was correct. The lung did not expand nor collapse with tracheal insufflation and necessarily interfered with exposure. When the upper lobe was gently retracted anteriorly and mesially, one could see a large pulsating hematoma in the superior mediastinum and in the region of the hilum of the lung posteriorly. As the lung was lifted forward, clotted blood began to extrude from one portion of the hematoma. It was feared that the chance of treating the patient successfully was almost nonexistent. By holding a finger over the point of rupture of the pulsating hematoma, the operator fortunately could quickly isolate the descending aorta at the level of its origin from the arch and place a clamp across it. Just as this was done, the remainder of the clot in the pulsating hematoma was extruded and brisk bleeding occurred. An index finger was introduced into the pulsating hematoma and then into a large channel, which proved to be the patent ductus arteriosus, and at the same time the descending thoracic aorta below the pulsating hematoma was compressed with the little finger. It was obvious that the main left bronchus was completely obstructed and one could see extravasation of blood in the lung itself. It was apparent that there was also some persistent bleeding from the hilum of the lung, that hemorrhage could not be controlled without a pneumonectomy, and that adequate exposure of the vascular structures necessitated this procedure also. Consequently, a clamp was placed across the hilum of the lung and, as soon as this was accomplished, the bleeding from the lung ceased. We were then able to dissect out the descending aorta distal to the aneurysm and place a clamp across it. The area was now dry except for some bleeding from intercostal and bronchial vessels and these were quickly clamped. The lung was now removed. First the thick-walled patent ductus arteriosus, about a centimeter in diameter, was divided between transfixing ligatures. The superior and inferior veins were next isolated and similarly treated. The main pulmonary artery was then transected between transfixing ligatures, following which the bronchus was divided and the lung amputated. We could subsequently ligate the clamped intercostal and bronchial vessels. A nylon filter fabric graft was interpolated between the base of the arch and the distal thoracic aorta. The opening in the base of the aorta was made large enough to permit the use of a graft with a circumference of 5 centimeters. The graft was approximately 17 centimeters in length. The patient had lost an enormous quantity of blood particularly during the first portion of the operation, a measured loss of 5,100 cubic centimeters. Blood had been replaced as rapidly as was possible. The mediastinal pleura was reapproximated over the distal end of the arch and the subclavian artery, but there was none available for covering the graft itself.

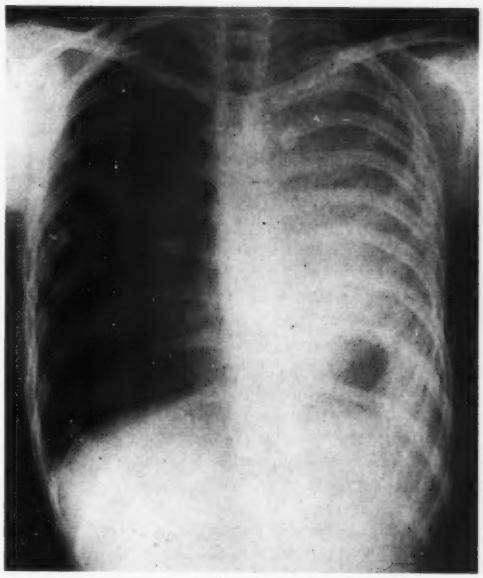

FIG. 2. Postoperative roentgenogram in Case 1.

The chest was closed in the usual fashion with interrupted silk sutures. The patient awakened promptly at the completion of the operative procedure and had no difficulty with motor or sensory power in his lower extremities. The aorta had been clamped for approximately 2 hours. Blood pressure had been maintained at a satisfactory level throughout. It was now approximately 145/90.

The cultures drawn the night of admission were all positive for hemolytic Staphylococcus aureus. The patient had received 1,000,000 units of crystallin penicillin the following morning and another 1,000,000 units prior to operation.

Due to the circumstances of the operative procedure, the specimen was somewhat distorted, but on careful examination it was evident that we were dealing with a postductal coarctation. The orifice through the area of coarctation was pinpoint in size. The intimal surface of the aorta was smooth but that lining the ductus was roughened and there were several small thrombi present. The false aneurysm had developed because of rupture of the ductus a very short distance from the point of attachment to the aorta. There were the remains of the poorly organized, pulsating hematoma. The lung was extensively damaged. The arteries and veins were patent, but the main stem bronchus was filled with dull, gray-black, friable blood clot. There was hemorrhage into the lung, particularly into the upper portion of the lower lobe. The pleural surface was ulcerated, and there was some necrosis. Bacterial colonies were easily visualized. The pulmonary arteries and arterioles were sclerotic.

The patient was given 1,000,000 units of crystallin penicillin intramuscularly every 2 hours postoperatively. On the eighth day the same dosage was administered every 3 hours and this was continued until July 13, when it was changed to every 4 hours. On July 17 it was reduced to 500,000 units every 4 hours and penicillin was discontinued on July 20. Up until this time he had also received 500 milligrams of streptomycin twice daily. The patient had done exceedingly well from the time of operation. The day following operation he had begun to eat and had a better appetite than he had ever had before. His temperature never exceeded 100 degrees and was generally normal. Blood cultures were repeatedly negative, as were several cultures of fluid removed for culture from the left pleural space. Two days after discontinuing the antibiotic therapy, the temperature rose to 101 and the blood culture again became positive for a coagulase positive hemolytic Staphylococcus aureus. The organism had proved sensitive to most of the antibiotics tested. The patient was again administered penicillin and streptomycin, which on July 25 was changed to ilotycin and achromycin. His temperature became normal and he was discharged from the hospital on August 6 with advice to continue taking 250 milligrams of ilotycin and 250 milligrams of achromycin every 6 hours for a period of 3 weeks. He remained afebrile. When seen on September 11 he was feeling well, had been without drugs for some time, and continued to have no fever. He now weighed 102 pounds, in contrast to 84 pounds upon admission.

On September 25 fever again developed, and the following day he was admitted to the hospital with a temperature of 103.2 degrees. Nothing unusual was found upon physical examination and the roentgenographic appearance of the chest was unchanged (Fig. 2). Blood cultures were again positive for the same organism. He was treated with ilotycin and achromycin, his fever rapidly subsided, blood cultures became negative, and he was discharged to his home on October 4, to continue the same medication for a period of 6 weeks. He remained afebrile and apparently in good health. When seen on December 2 he weighed 110 pounds. He had been without medication for several weeks and was afebrile.

He had to be readmitted to the hospital on December 30 because of another onset of fever. Temperature at the time of admission was 104. Again, blood cultures were positive for coagulase positive Micrococcus pyogenes. The organism was still sensitive to a variety of antibiotics. Physical examination was essentially unchanged except that in contrast to what had previously obtained, his femoral, popliteal, dorsal pedal, and posterior tibial pulses were now quite weak and blood pressure in the lower extremities was substantially less than that in the upper extremities. It was our opinion that we now had very suggestive evidence that he had an infected thrombus in the graft or at the suture line causing partial or complete obstruction. Consequently, after intensive treatment with achromycin and ilotycin, 250 milligrams every 6 hours, a regimen which brought about a rapid subsidence of his fever and a return to negative of his blood cultures, he was operated upon on January 8. The residual left thoracic cavity was filled with heavy scar tissue and it was quite difficult to dissect down to the region of the graft. Once this area was encountered, it was noted that the graft was surrounded with a very small amount of purulent material. A smear revealed cocci. The graft was soft and pliable and throughout its extent we were unable, on compression, to feel anything resembling an intramural thrombus. The same held true with regard to the suture lines. It was obvious that the decrease in pulses distal to the graft was due to the fact that the heavy scar tissue had partially compressed and kinked the graft. After the surrounding scar tissue had been removed and the graft had resumed its normal contour, pressures and pressure pulse tracings were essentially the same in the aorta proximal and distal to the graft. An extensive thoracoplasty was carried out with wide resection of the second through the ninth ribs. The residual chest wall now seemed to collapse nicely against the graft and the mediastinal pleura. The area was drained with 2 large empty Penrose drains brought out through an incision in the inferior portion of the residual cavity. Postoperatively he did well. He was given 12,000,000 units of penicillin and ilotycin through continuous intravenous drip daily until January 31 when intramuscular penicillin, 2,000,000 units every 4 hours, was given instead. It was altered on February 5 to 600,000 units of penicillin every 8 hours intramuscularly and 250 milligrams of achromycin every 6 hours. He remained afebrile and was discharged from the hospital on February 18. Blood cultures were repeatedly negative.

When seen on March 31 he looked well. The pulses were excellent in the femoral, dorsal pedal, and posterior tibial arteries. Blood pressure in the right arm was normal. He had remained afebrile and asymptomatic since discharge.

He was readmitted to the hospital on April 29. Two days beforehand he had begun to have a low grade fever which had become high the night before admission. Some pain had developed in the left side of the chest. Except for fever, general examination was essentially normal. Blood culture was again positive for Staphylococcus aureus. This time the organism was coagulase negative. It was still sensitive to a number of antibiotics but now was resistant to penicillin. He was placed on large doses of ilotycin. Unlike the course on previous occasions, however, there was now no response to antibiotic therapy and fever continued. X-ray studies revealed no change from the situation previously noted. On May 7 severe pain suddenly developed in the left side of the chest. When examined shortly thereafter he was seen to have a huge, pulsating hematoma involving the left hemithorax. In a

very short while there was ecchymosis of the skin, particularly in the region of the old thoracotomy incision. It appeared evident that the pulsating hematoma was the result of rupture of a mycotic aneurysm.

From the moment the initial operation had been completed, we had been faced with the possibility, and later the actuality, of recurrent infection. Now the situation seemed even more hopeless. There appeared little likelihood of successfully managing the expanding, pulsating hematoma, and if this could be accomplished we still had before us the problem of infection. The boy's parents were anxious that everything possible be tried. It was obvious that there was no hope of approaching the lesion through the left hemithorax without exsanguination. Another plan was consequently adopted.

Since the temperature was markedly elevated, the patient was cooled to 34 degrees centigrade in ice water after anesthesia had been induced. A T-shaped incision was made over the sternum and extended downward almost to the umbilicus. The sternum was split in the midline throughout its length and the abdominal wall was opened in the midline. After incising the pericardium longitudinally, the diaphragm was split back to the aortic hiatus. The triangular ligament of the left lobe of the liver was severed and the lobe retracted to the right. There was now excellent exposure of the ascending aorta and of the distal thoracic and upper abdominal aorta (Fig. 3). One could feel the pulsating hematoma extending down to about the level of the eleventh intercostal artery. After freeing the distal thoracic and upper abdominal aorta, a stretch weave dacron graft was sutured end-to-side to the distal portion of the thoracic aorta below and to the ascending aorta above. When the partial exclusion clamps were removed the graft pulsated well. With some difficulty the arch was now dissected free to a point distal to the left carotid artery. The arch was then divided between the carotid and subclavian arteries and the two ends were closed by suture. The descending thoracic aorta was similarly divided and sutured just proximal to the attachment of the graft below. Now the pulsating hematoma was excluded from the circulation, save for connection through the left subclavian and possibly an intercostal artery or so. The pericardium and the diaphragm were reapproximated leaving the graft within the pericardial sac. The sternum was brought together with wire sutures and closure of the wound was completed. A catheter was brought out from underneath the sternum for under-water seal drainage. The patient had withstood the procedure well. The pleural cavities had not been entered.

He was now turned on his side and the old posterolateral incision was quickly opened. The pulsation of the hematoma had ceased. The large clot was evacuated. At the lower graft-aortic anastomosis there was found a small, recently ruptured, mycotic aneurysm. The graft was clamped and detached below. A little

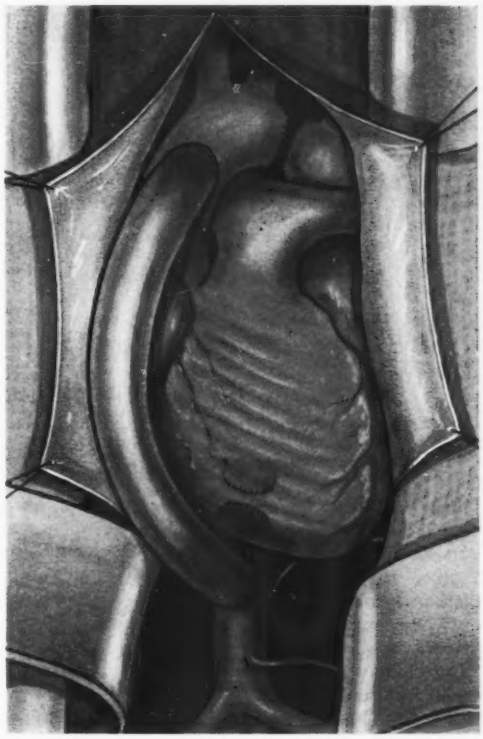

FIG. 3. Diagrammatic sketch showing the operative exposure, the graft, and the aortic division carried out at the second operation in Case 1.

bleeding occurred into the distal isolated aortic segment, apparently from a small intercostal vessel. The end of the aorta was closed by suture. The graft was now freed proximally. As we approached the point where it was sutured to the base of the subclavian, the graft was inadvertently torn loose. The open base of the subclavian retracted deeply within a rigid hole in the residual pleural scar tissue. Bleeding was easily controlled with an oxycel pack, and since dissection of the subclavian from its encasing heavy scar would have been very difficult, it was decided to leave a pack in place. It was further secured by packing the residual pleural space with curlex bandage and closing the muscle and skin over it. It was planned later to reopen the wound, remove the pack, and, if bleeding occurred, to dissect out and ligate the subclavian artery. The measured blood loss during the procedure was 2,300 cubic centimeters, and this was replaced with an equal amount of blood.

The patient looked extraordinarily well after operation. The next day his temperature fell to normal and did not become elevated again. The blood pressure was stable, around 130/70. The hemoglobin was 11.5

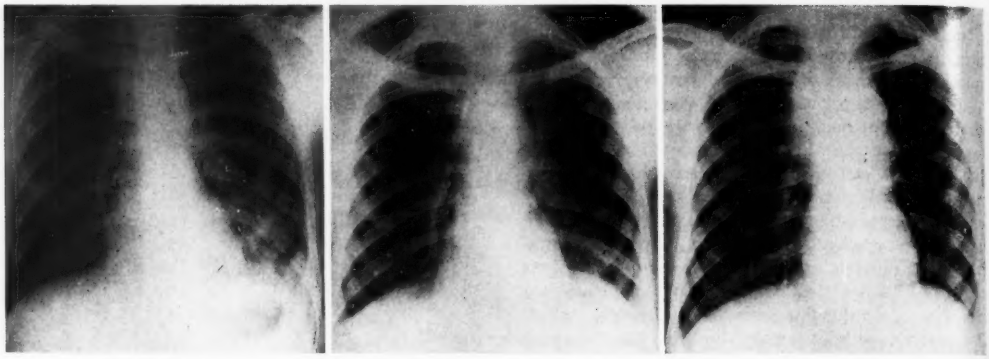

FIG. 4. Roentgenograms of the chest in Case 2 which were taken on November 8, November 13, and December 2, 1957.

grams. Later the evening of the day of operation a 500 cubic centimeter transfusion was given. The next day he seemed well. He was eating and voiding adequately. Because his hemoglobin was now 10 grams, he was given a pint of blood that morning and another that evening. Early the following morning the blood pressure, which had been around 140/70, slowly began to rise to a level of 180 systolic. He seemed comfortable and ate his breakfast heartily. Shortly afterward rapid respiration and a persistent cough developed. His color remained good for a while, and then he became cyanotic. At this time breath sounds on the right side were good. There was no evidence of pulmonary edema. Suddenly the blood pressure rose rapidly to a level of over 250 systolic and his pulse to about 125. At this time his femoral pulses were bounding and the cause of the sudden hypertension was unknown. While he was being examined he began to bleed profusely from the left thoracotomy wound. He was picked up and taken immediately to the operating room, while pressure was applied over the chest wound. However, by the time he could be placed on the operating table and anesthetized, cardiac arrest had occurred. It was not possible to bring about resuscitation in spite of reopening the mediastinal wound and carrying out cardiac massage.

The postmortem examination showed moderate atelectasis of the right lung and bronchopneumonia. All lobes had reduced crepitance and presented a purplish red, meaty appearance on cut section. A small amount of sanguineous fluid could be expressed from the cut surfaces. Microscopic examination revealed many alveolar spaces to be filled with exudate, including fibrin, macrophages, and neutrophils. The exudate extended into interalveolar septa. There were hyaline-like membranes lining some alveoli. The left subclavian artery and the fragment of aorta attached to it had retracted far upward toward the axilla. It appeared that reduction in effective functioning lung tissue had caused carbon dioxide retention and hypoxia with resultant marked hypertension and bleeding.

CASE 2. The patient was a 17½ year old male who had been in an automobile accident on November 8, 1957. He was unconscious for a short while. On admission to another hospital he complained of pain in his chest, made worse by deep breathing. He had x-ray evidence of fractures of several ribs on the left. He continued to complain of chest pain but was not cyanotic and only mildly dyspneic and was discharged to his home on November 14. He continued to complain of chest pain, had some difficulty in swallowing, took only liquids, and occasionally he vomited. On November 28 he vomited blood for the first time. The next day a cough developed and he had so much difficulty in swallowing that he refused all oral intake. On November 30 he was very dyspneic. By December 2 he was extremely hoarse. The cough and dyspnea became worse and he was readmitted to the same hospital and the next day was transferred to our institution. Roentgenograms brought with him showed progressive mediastinal widening (Fig. 4).

He was a critically ill young man. He looked somewhat emaciated, was having great difficulty in breathing sitting straight up in bed, was mildly to moderately cyanotic and so hoarse and short of breath that he could hardly speak. His temperature was normal, pulse 120, blood pressure 155/80. Breath sounds were good on the right side, absent on the left. The left hemithorax was hyperresonant. Indirect laryngoscopy revealed a left vocal cord paralysis. While his blood was being cross-matched, roentgenograms were obtained. These revealed evidence of trapped air in the left lung, a large mass in the superior mediastinum extending somewhat to the left and even more so to the right, with marked displacement of the esophagus to the right and nearly complete obstruction, almost complete tracheal compression, and recent fractures of the seventh, eighth, and ninth ribs on the left posterolaterally (Fig. 5). The patient seemed almost

FIG. 5. Roentgenograms made on admission in Case 2. The large mediastinal mass, the esophageal displacement and compression, and the extreme tracheal narrowing are seen. The radiolucency of the left lung evident on the films is not clear on the reproductions.

moribund and it appeared doubtful that we could obtain adequate quantities of cross-matched, freshly drawn blood, set up for the pump bypass, and begin operating before he expired of asphyxia. He was, however, in the operating room in less than 3 hours. He was so dyspneic and orthopneic, anesthesia had to be induced with him sitting straight up. A catheter was placed in the right radial artery for direct pressure recording. A left femoral incision was made. The vena cava was catheterized via the stump of the saphenous vein for infusion purposes and a large inflow cannula was placed through an arteriotomy into the femoral artery, after the administration of intravenous heparin. A left posterolateral thoracotomy was made and the chest was entered through the fourth interspace. There was complete left bronchial obstruction and the trapped air in the lung made exposure difficult. There was a bulging of the aorta just beyond the subclavian and a huge pulsating hematoma posterior to it and extending toward the right. The pericardium was opened and a large outflow catheter was placed into the left atrium through its appendage and secured in place. The two catheters were now connected to the pump. The left subclavian artery was isolated some distance to the point of its origin and a tape was placed about it. Working both within and without the pericardium, we were able, with some difficulty, to free the pericardium from the arch of the aorta and to dissect free the arch between the level of the left carotid and subclavian arteries. The descending aorta distal to the pulsating hematoma was isolated. It was necessary to divide one intercostal artery. The arch between the carotid and the subclavian, the left subclavian artery, and the descending aorta were now cross-clamped and the pump bypass begun. The aneurysm was opened and a large clot evacuated. The main dissection had occurred posteriorly and to the right, and the residual cavity after evacuation of the clot was about 12 to 15 centimeters in diameter. There was a transverse tear of the aorta posteriorly just beyond the origin of the subclavian artery and the rent extended distally about 2.5 centimeters. The involved segment of the aorta was excised. After removing all clots and irrigating out the cavity, we could see a longitudinal pressure laceration of the esophagus about 5 or 6 centimeters long. On inspecting the lumen of the esophagus, pressure ulcers could be seen on the opposite wall. They appeared to be superficial. The margins of the laceration were excised and it was closed with inverting No. 4-0 arterial silk sutures. A stretch weave dacron graft was then sutured to the arch immediately adjacent to the subclavian artery and to the aorta below. When the clamps were released the graft worked well. The pump bypass was stopped. As soon as the hematoma had been evacuated, the lung had begun to expand and collapse nicely with compression and release of the anesthetic bag. The wound was repaired by ap-

FIG. 6. Barium swallow in Case 2 showing extraesophageal passage of barium into a small mediastinal cavity. Films a few moments later revealed complete emptying of this barium back into the esophagus.

proximating the ribs with several catgut sutures and closing the remainder of the wound in layers with interrupted silk sutures. A gastrotomy was performed. By means of a Levin tube passed down through the nasopharynx, a string was brought out through the nose above and alongside the gastrotomy tube below.

The patient did very well thereafter. In spite of the fact that a chest tube had been left in place at the time of operation, it was impossible to keep the left hemithorax free of pleural fluid. However, this presented no problem and the patient breathed without difficulty. He became nearly afebrile on December 8 and completely so after December 16. He never exhibited cyanosis. His hoarseness continued. He had no oliguria. Indeed, he put out 375 cubic centimeters of urine the day of operation and a liter the following day. Gavage feedings were started on December 9. He had no difficulty in swallowing and so on December 11 water was allowed orally, and the next day liquid diet. On December 17 he had a barium swallow. Much to our surprise this demonstrated that a leak had occurred at the site of the esophageal suture. The extraesophageal cavity, however, readily delivered the barium back into the esophagus and thus cleared itself. His oral feedings were discontinued. He was discharged from the hospital on gastrotomy feedings on December 24.

We were puzzled as how best to manage the esophageal leak. Since the barium swallow demonstrated that the material not only entered the cavity readily, but emptied itself back into the esophagus almost immediately, and since the size of the cavity seemed to be getting progressively smaller, it was thought advisable to leave the situation alone, hoping that the cavity would gradually scar down with closure of the esophageal opening.

He was seen again on January 9. He had continued on his gastrotomy feedings, had gained 5 or 6 pounds, remained afebrile, and looked well. Barium swallow on this day revealed the cavity about the esophagus to be smaller and still to be emptying promptly back into the esophagus. He was now given liquids orally.

He was readmitted to the hospital on January 21. He stated that on January 19 he had developed chills and fever and general malaise. The following day he had become anorexic. It was obvious that he had mediastinitis. A barium swallow showed no essential change (Fig. 6). His temperature was 104.5 degrees. The following day the posterior portion of the sixth rib and its transverse process were resected and the posterior mediastinum was drained with an empty, soft Penrose drain. Temperature fell to normal and did not rise above 99.6 until January 28 when it rose to 101.2. It was obvious that the mediastinitis had not been adequately drained. Consequently, the following morning a short segment of the posterior portion of the fifth rib and its transverse process were removed and more adequate mediastinal drainage was established. He did reasonably well until the late afternoon of the following day when he vomited 275 cubic centimeters of bright bloody fluid. With the administration of blood he made a good response, and the blood pressure stabilized at 120 systolic. Early in the morning, however, he became nauseated and began to vomit huge quantities of bright blood. Esophageal balloon tamponade was immediately instituted and he was taken directly to the operating room.

A right thoracotomy was performed. The tissues about the damaged portion of the esophagus were friable and densely scarred. After the azygos vein was divided between ligatures, the esophagus was exposed. A large quantity of bright blood escaped from within the lumen of the esophagus in spite of the inflated balloon. The balloon was deflated and removed, and the esophagus was quickly mobilized. In doing this, apparently one of the paravertebral veins must have been torn, for now there was brisk bleeding not only from the esophagus itself but from the paraesophageal area. Before the bleeding could be brought under control the patient expired. Postmortem examination revealed extensive inflammation of the esophagus and the surrounding tissues. The specific site of the bleeding could not be definitely identified.

DISCUSSION

The etiologic factor causing the pulsating hematoma in the first case was rare. We

have not found described a case quite like it. One case has, however, been recorded by Cope and Ellison in which pneumonectomy was required because of massive pulmonary infarction in a patient who had an infected patent ductus arteriosus not associated with coarctation of the aorta. The etiology of the second case was one not infrequently seen.

In dealing with the initial emergency in the first case, it was apparent from the fact that the patient had coarctation of the aorta that he would almost certainly withstand prolonged aortic clamping without ill consequences. It was obvious that the procedure was attended with hazard and that there was a possibility that we could not gain control of the proximal and distal aorta and of the patent ductus arteriosus before too much blood would have been lost. No other approach, however, occurred to us as a possibility at that time. In retrospect, it is quite clear that we were exceedingly lucky in being able to isolate the proximal aorta before the pulsating hematoma ruptured widely into the pleural space, and subsequently, to control by digital pressure the other bleeding points until the hilum of the lung could be cross-clamped and the distal aorta isolated and occluded. We know of no way in which the recurrent bacteremia and the ultimate endarteritis and development of the distal mycotic aneurysm could have been obviated. At the time of the later operation, it was evident that the situation could not be handled safely by direct approach through the residual left pleural cavity. The procedure utilized proved to be one that was technically not too difficult and permitted us to re-establish aortic continuity and to isolate the pulsating hematoma by proximal and distal aortic division before approaching the hematoma directly. The decision to control bleeding from the isolated distal stump of the open subclavian artery by packing seemed the correct one at the time. In view of the fatal exsanguination that ultimately occurred during the patient's hypertensive episode, it is evident that we would have been wiser to prolong the operation still further and to isolate and ligate this vessel. It is doubtful from the apperance of the remaining right lung at postmortem examination that we could have safely brought him through this complication under any circumstances. It is further doubtful that we could have obviated recurrence of the same sort of difficulty from his staphylococcal bacteremia had he survived this episode.

The second case presented a different problem and one which will undoubtedly be more commonly encountered in the management of rapidly expanding, pulsating hematomas within the thorax. Here we were dealing with a false aneurysm developing in a patient who did not have coarctation and whose aorta could therefore not be safely clamped for an adequate period of time. It was necessary, therefore, to use some adjuvant to permit temporary aortic occlusion with safety. In our experience, the use of hypothermia in this respect has not proved nearly so effective from the experimental point of view as a measured bypass of oxygenated blood into the distal arterial segment during aortic cross-clamping (5). Furthermore, our clinical experience has proved the latter method to be attended with far greater success than the use of hypothermia. Our initial clinical experiences with such a measured bypass, utilizing blood-bank blood, convinced us that it was preferable to use only relatively freshly drawn blood for such purposes. If this assumption is correct, the problem of getting set up for such an operation is made a little more difficult. It is necessary not only to prepare in a short period of time the materials necessary for the bypass itself, but also to obtain cross-matched, freshly drawn blood. The patient was in such desperate condition and so near asphyxia from tracheal compression that it seemed not unlikely that he might expire before such preparations could be made. Fortunately, however, the operative procedure was carried out soon enough and the patient withstood it quite well. Had we managed his compression in-

jury of the esophagus better, the patient would undoubtedly have survived. His ultimate death was not related in any way to the resection of the aneurysm and the interpolation of the graft, but was the direct consequence of the esophageal leak and the resultant mediastinitis. Just how the esophageal problem should have been managed, we do not know. One alternative which might have worked better would have been to close the esophagus over a large T tube, bringing one limb of the T tube out through the posterior chest wall. Probably a safer method would have been to resect the damaged portion of the esophagus, close its distal end, and perform a cervical esophagostomy with the view to reconstructing the esophagus later.

As we look back over this operative experience, it seems to us obvious that though in this case we were able to gain control of the aorta proximal and distal to the site of rupture, one could not anticipate that this would be possible in every instance. It therefore raises the question whether in cases of this sort it might not be safer in the long run to utilize the second procedure carried out in the first patient. One would initially perform a mediastinotomy and upper midline abdominal incision and insert a permanent bypass from the ascending aorta to the distal portion of the descending thoracic aorta and then proceed to dissect out the arch as far as could safely be done and to divide and close it. Similar division of the descending thoracic aorta proximal to the graft would isolate the pulsating hematoma and permit a safer approach through the opened thorax. The experience of Murdock emphasizes the fact that the direct transthoracic approach to the pulsating hematoma may be fraught with great hazard of fatal exsanguination while efforts are being made to gain control of the aorta proximal and distal to the site of rupture. There is every reason to believe that a graft interpolated between the ascending aorta and the descending thoracic aorta in the fashion described would prove satisfactory. We are at the present time checking its long-term feasibility in experimental animals. The initial results indicate that these will be successful. Permanent bypass grafts have, of course, been used by others. For example, Adams in 1955 utilized a permanent homograft from left subclavian to descending aorta in treating successfully a traumatic aneurysm of 1 year's duration. In their large experience with aortic aneurysms, DeBakey and his associates have also used permanent bypasses in various situations. As far as I know, no one has, to date, reported utilization of a permanent aortic bypass within the mediastinum and upper abdomen for the purposes which were employed in our case.

It is clear from the experience with our second patient and from other cases similar in nature reported in the literature that every effort should be made, in the case of all severe thoracic injuries, to determine as early as possible whether there is any evidence of aortic rupture and to watch such patients with great care. It will undoubtedly continue to be a very real problem to decide whether in such cases one can continue a policy of watchful waiting for a while, hoping that the pulsating hematoma will not expand rapidly but will with the passage of time develop into a chronic saccular aneurysm which can be treated by election later on, or whether, on the other hand, rapid expansion will occur with threat to the patient's life either from the standpoint of rupture and exsanguination or interference with pulmonary and esophageal function.

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THE EFFECT OF TRAUMA AND TRANSPLANTED TISSUES ON THE APPEARANCE OF LEUKEMIA IN MICE FOLLOWING TREATMENT WITH METHYLCHOLANTHRENE

CREIGHTON A. HARDIN, M.D., F.A.C.S., and ALVAR A. WERDER, Ph.D.,
Kansas City, Kansas

WE HAVE REPORTED previously (1) the observations of local development of squamous cell carcinoma in a purebred strain of DBA/1 mice painted with methylcholanthrene. The transfer of normal appearing ventral skin to untreated DBA/1 mice resulted in lymphosarcoma.

We also have reported (2) that surgical incisional trauma to distant untreated skin potentiates induced squamous cell carcinogenesis in skin areas painted with methylcholanthrene in DBA/1 mice. Animals painted for 3 weeks before being traumatized showed a tumor incidence of 16 per cent as compared with an incidence of 3 per cent in the nontraumatized group. A group painted and traumatized for 6 weeks showed a total tumor incidence of 70 per cent compared with 10 per cent in the nontraumatized control group.

This report describes the effect of trauma and of transplanted tissues upon the appearance of leukemia in DBA/1 mice following treatment with the use of methylcholanthrene.

METHOD

Experiment A. The effect of methylcholanthrene and trauma on the appearance of leukemia in DBA/1 mice. A 0.6 per cent solution of 20-methylcholanthrene in a reagent grade of benzene was applied to the dorsal unepilated interscapular skin of DBA/1 mice with a No. 4 camel's-hair brush. A single stroke delivered about 0.1 milligram of methylcholanthrene. Paintings were done on 141 DBA/1 mice 3 times weekly for 3, 6, 9, or 12 weeks. All of these animals were observed for 10 months after the completion of skin paintings. Leukemia appeared 5 to 10 months after the application of methylcholanthrene had been stopped. Spontaneous leukemia has not been observed in DBA/1 mice by us or the breeders. Trauma consisted of a 1 centimeter surgical incision through the full thickness of the unpainted midline belly skin. The incision was then resutured with No. 4-0 black silk. The time of trauma varied from immediately to 2 months following the completion of methylcholanthrene skin painting. Leukemia appeared 4 to 7 months after the completion of skin painting for 3 and 6 weeks and at 1 to 2 months after completion of methylcholanthrene painting for 9 and 12 weeks.

Experiment B. The effect of tissue transplantation from methylcholanthrene treated DBA/1 mice on the appearance of leukemia when transferred to untreated DBA/1 mice. Donor DBA/1 mice were painted with methylcholanthrene as in Experiment A with the same time interval, location, and amount of carcinogen. At the completion of the 3, 6, 9, and 12 week paintings, tissues from the painted animals were transplanted to 89 untreated DBA/1 mice. Five to 6 animals in each of these painted groups served as the donor source of transplanted tissue. The time of tissue transfer following the completion of methylcholanthrene painting was immediately or at 1 or 2 months.

The following tissues were obtained from

From the Departments of Surgery and Microbiology, University of Kansas Medical Center, Kansas City, Kansas.

TABLE I.—EXPERIMENT A, EFFECT OF METHYLCHOLANTHRENE AND TRAUMA ON LEUKEMIA IN DBA/1 MICE

Time of application (3 times weekly)	*Time of trauma following MC application*	*No. with leukemia*	
		Trauma	*No trauma*
3 weeks	Immediately	0/10	0/30
	1 month	3/10	—
	2 months	0/10	—
6 weeks	Immediately	2/10	0/30
	1 month	1/10	—
	2 months	4/10	—
9 weeks	No trauma	—	2/6
12 weeks	No trauma	—	7/15

methylcholanthrene-treated mice and transplanted to untreated DBA/1 mice. All skin grafts were taken from the unpainted ventral belly surface of previously dorsally painted DBA/1 mice.

1. Full thickness skin grafts, 1 centimeter square, were sutured into a patterned dorsal surgical defect of the recipient. All subcutaneous tissue was removed by sharp dissection.

2. Thin split skin grafts, 1/10,000 of an inch and dermal skin grafts were obtained by gluing a full thickness skin to a Padgett-Hood dermatome and mechanically splitting the skin. Each of these 1 square centimeter grafts was implanted subcutaneously. The graft was folded with the raw surfaces facing out and placed through a dorsal incision and resutured.

3. Spleens were divided into 3 equal parts and placed through a surgical incision in the right flank of the recipient animal. This incision was resutured.

4. Painted donor DBA/1 mice were bled. The blood was allowed to clot and 0.1 milliliter of supernatant serum was injected intraperitoneally into donor mice.

Grossly, at autopsy the animals with leukemia showed generalized adenopathy, splenomegaly, and liver congestion. Marrow studies were done to confirm the diagnosis of lymphatic leukemia. The femurs were denuded of tissue, ends clipped, and the marrow expressed under pressure with a saline syringe attached to a No. 27 needle. Smears of bone marrow so obtained were prepared with Wright's stain. Impression smears of the cut surfaces of the spleen were also made with Wright's stain. Routine sections and staining with hematoxylin and eosin were made of all grossly abnormal tissues.

RESULTS

Surgical trauma distant to the site of previous skin painting enhanced the appearance of leukemia. Leukemia developed in 10 of 60 traumatized mice. A comparable nontraumatized group showed no leukemia. Only the 3 and 6 week painted mice are compared since the nontraumatized mice painted for 9 and 12 weeks represent the critical time exposure and dosage of the carcinogen for the appearance of leukemia (Table I).

The transfer of ventral unpainted skin from mice previously painted at a dorsal site resulted in the appearance of leukemia

TABLE II.—EXPERIMENT B, EFFECT OF TISSUE TRANSPLANTED FROM MC TREATED DBA/1 MICE ON THE APPEARANCE OF LEUKEMIA WHEN TRANSFERRED TO UNTREATED DBA/1 MICE

Time of application (3 times weekly)	*Time of tissue transfer after MC was stopped*	*No. with leukemia/Total*				
		Full thickness skin	*Thin split skin graft*	*Dermal skin graft*	*Spleen*	*Serum*
3 weeks	Immediately	1/10	—	—	2/10	0/10
	1 month	3/10	—	—	2/10	0/10
	2 months	0/10	—	—	3/10	0/10
6 weeks	Immediately	5/10	—	—	2/10	0/10
	1 month	4/10	—	—	2/10	0/10
	2 months	0/10	—	—	—	1/10
9 weeks	1 month	0/10	4/8(1*)	0/7	3/9	0/10
12 weeks	1 month	5/10(1*)	—	—	6/9	0/8
	2 months	5/9(2*)	7/7(7*)	6/8(6*)	—	—

*Lymphosarcoma present locally.

in the isologous recipient. Transplanted full thickness skin grafts resulted in the appearance of leukemia in 23 of 89 mice. Lymphosarcoma also developed locally in 3 of 19 animals. Thin split grafts, primarily epithelial elements, showed leukemia in 11 of 15 transplants. Lymphosarcoma locally appeared in 8 of 15 mice. Dermal skin grafts developed leukemia in 6 of 15 animals and lymphosarcoma in 6 of 6 mice.

Splenic transplants resulted in the appearance of leukemia in 20 of 58 mice. Serum showed only a single instance of leukemia in a total of 78 injections (Table II).

DISCUSSION

Acceleration of induced squamous cell skin cancer and leukemia seems to be potentiated by trauma distant to the site of applied carcinogen. The well known enhancement of local trauma to the same areas of skin exposed to carcinogens could be explained by the additive effects of irritation.

The inducement of lymphosarcoma resulting from the transplantation of skin grafts treated with methylcholanthrene may be an expression of a systemic effect of the carcinogen. The transfer of full thickness, dermal, and thin split grafts was done in order to determine if a transferable agent was localized in any particular layer of skin. Leukemias developed from the transplantation of all types of these skin grafts. It is of interest also to note again the local appearance of lymphosarcoma at the site of transplanted skin graft along with leukemia. The spleen also contained a substance capable of producing leukemia on transplantation. Cell free serum showed only 1 instance of leukemia when injected.

More recent experiments with both a cellular and filtrate inoculum have resulted in the appearance of transference of leukemia in mice when passed as many as 6 times. Tissue culture experiments also indicate the presence of a filterable agent. These observations of leukemia transfer have led us to think that we are dealing with a virus or virus-like agent. It is highly probable that the local application of a carcinogen such as methylcholanthrene produces not only a localized squamous cell cancer but also more complex and generalized systemic changes in tissues which appear grossly and even microscopically normal. It is only when transplanted to an isologous animal that the latent transferable agent manifests itself as a lymphosarcoma or leukemia.

SUMMARY

Surgical trauma distal to the site of skin previously painted with methylcholanthrene enhanced the appearance of leukemia.

Skin grafts of varying thickness, spleen, and serum obtained from DBA/1 mice painted with methylcholanthrene resulted in lymphatic leukemia and lymphosarcoma when transplanted to an unpainted homologous strain of mice.

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EFFECTS OF SEROTONIN (5HT) AND SEROTONIN PRECURSOR (5HTP) ON GASTRIC SECRETION IN THE DOG

THOMAS T. WHITE, M.D., F.A.C.S., ROBERT A. MacALEXANDER, M.D., and DONAL F. MAGEE, M.D., Ph.D., Seattle, Washington

In 1956, the studies of Black and his associates (1) demonstrated that serotonin, 5-hydroxytryptamine (5HT), inhibited acid secretion in dogs with simple gastric fistula, and the question arose as to whether or not this could be the antral inhibitory substance. Previous knowledge of surgical interest in regard to serotonin has been chiefly concerned with malignant carcinoid tumors.

Serotonin exists in particularly high concentrations in the mucosa of the duodenum and pylorus. It is present in lesser amounts in the fundus of the stomach, the jejunum, ileum, and colon. The presence of such great quantities of this substance in the normal antral mucosa has focused interest on the part that 5HT may play in the normal function of the stomach. Previous work by White and Magee (6) has shown that serotonin stimulated the production of pyloric mucin through a direct action on the mucosa. Further work by Black has shown that this is a diffuse effect on the stomach. Other work by Haverback (3, 4), Black (2), and ourselves (6, 7) has shown that serotonin tends to depress resting gastric secretion and raise *p*H slightly. Further work on histamine stimulated secretion by Black (2) has shown that this stimulus will also be partially inhibited by serotonin. Serotonin precursor, 5-hydroxytryptophane (5HTP), has been shown by Haverback and associates (3) to be rapidly converted to the depot form of serotonin and to inhibit the spontaneous acid and water secretion of the stomach.

The present report describes the effect of 5HT and 5HTP on the acid and pepsin secretion of resting Pavlov and Heidenhain pouches and those stimulated by feeding or histamine.

From the Departments of Surgery and Pharmacology, University of Washington, Seattle.

METHODS

1. Collections of secretion were made every 20 minutes in 9 to 12 kilogram Pavlov and Heidenhain pouch dogs fed 10 grams of horse meat every 10 minutes. The procedure was carried on for an hour or until a plateau of secretion had been achieved; 5HTP was then given in a single dose of 25 milligrams per kilogram intravenously or a continuous infusion of 20 gammas per minute of 5HT. Collections were made for another 100 minutes. The changes in rate of secretion and *p*H were measured.

2. Twenty minute collections of secretion were made in 9 to 12 kilogram Pavlov and Heidenhain pouch dogs stimulated with, at first, 0.02, then 0.1 milligram of histamine base every 10 minutes. The dogs were then given 25 milligrams per kilogram of 5HTP in 1 intravenous dose, or 20 gammas per minute of 5HT by continuous infusion. Collections were made for 100 to 120 minutes. The changes in rate of secretion, *p*H, and pepsin secretion were measured.

3. Two Heidenhain pouch dogs, 2 Pavlov pouch dogs, and 1 double pouch (pyloric-Heidenhain) dog were given a single intravenous dose of 5HTP, and the volume, *p*H, and pepsin production were compared with the plateau achieved during the previous 10 days. These results were compared with those in which a monamine oxidase inhibitor, beta-phenylisopropyl hydrazine (PIH), was used when juice was collected for 10 days, and the second period of 5 days, as comparison with the control.

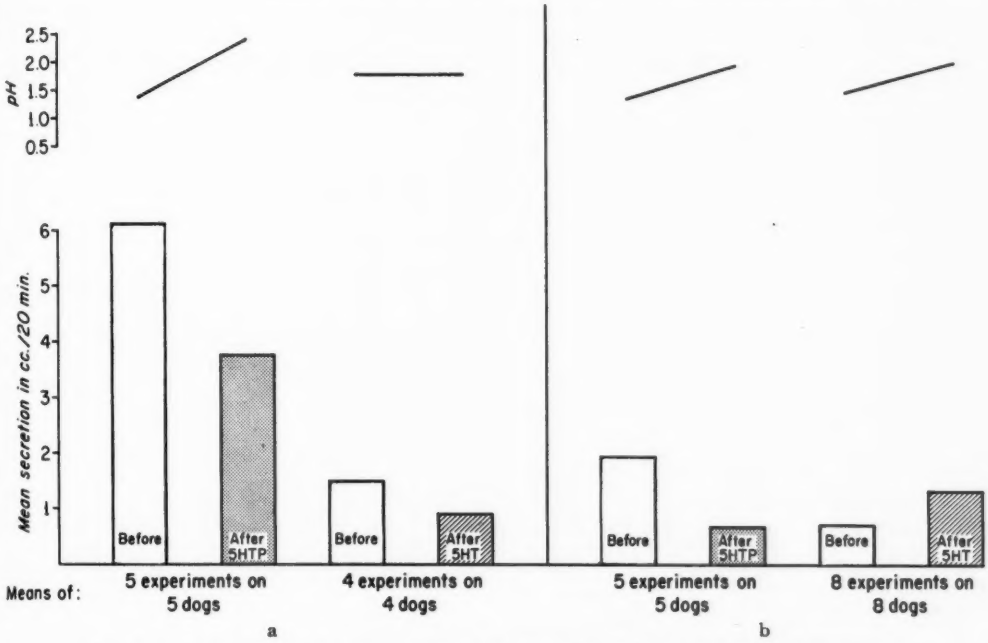


FIG. 1. Effect of 5HTP and 5HT on food induced secretion of Pavlov and Heidenhain pouches. a, A significant drop in the rate of water and acid secretion is noticed in Pavlov pouches after 5HT or 5HTP is given, and, b, no clear change in Heidenhain pouches. The rise in secretory volume in the Heidenhain pouches after 5HT is probably due to increased mucin production with little change in water or acid.

4. Reserpine, 1 milligram per kilogram, was given intravenously to 2 dogs having pyloric and Pavlov pouches. The expected hypersecretion was noted in the Pavlov pouches. Sixteen hours later this hypersecretion was still seen. In both dogs the pyloric pouches were irrigated with 0.1 normal hydrochloric acid. An intravenous injection of 5HTP was then given.

RESULTS

1. There was a significant drop in rate of secretion and rise in *p*H after administration of either 5HT or 5HTP to the food stimulated Pavlov pouch dogs. No significant changes were noted in Heidenhain pouch dogs under a similar regimen (Fig. 1).

2. There were no significant changes in histamine stimulated secretory volume or *p*H after administration of 5HT or 5HTP either with large or small doses of histamine. The pepsin production was, however, significantly increased in Pavlov pouches after 5HTP (Figs. 2 and 3).

3. There was a marked increase in volume and pepsin production in 24 hour collections in 5 dogs with fundic pouches after administration of a single dose of 5HTP with a significant drop in acid production in comparison with control collections. A similar effect was noted with the monamine oxidase inhibitor (PIH) in a later experiment using the same dogs (Fig. 4).

4. 5HTP in 1 dog did not detectably affect the reserpine-stimulated hypersecretion of the Pavlov pouch, although gastric mucin did appear in increased quantity. Pyloric inhibition of Pavlov pouch secretion by hydrochloric acid was not seen after an intravenous dose of reserpine and did not return after the administration of 5HTP or 5HT 24 hours later.

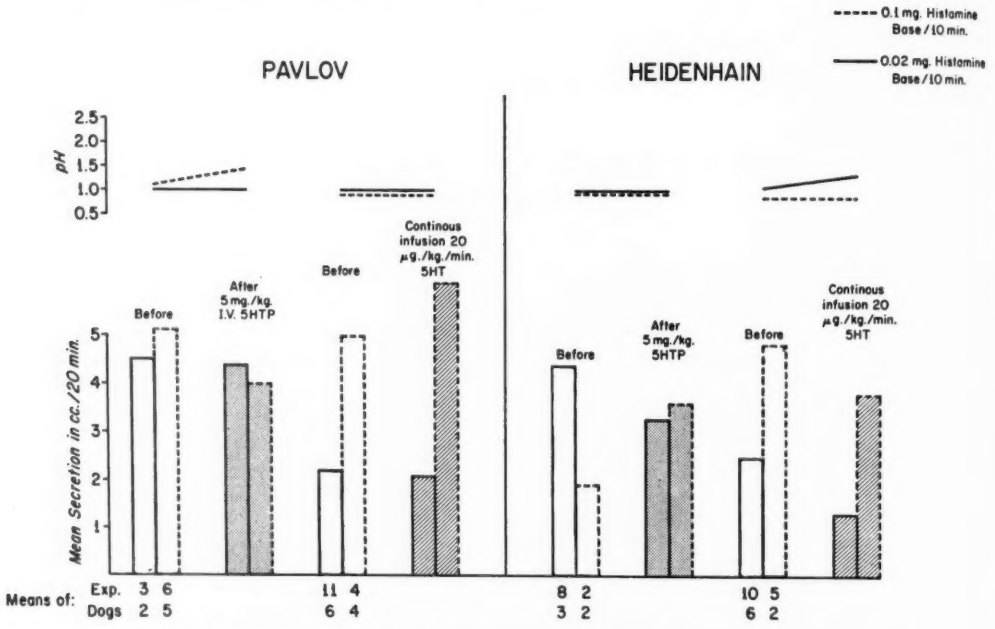


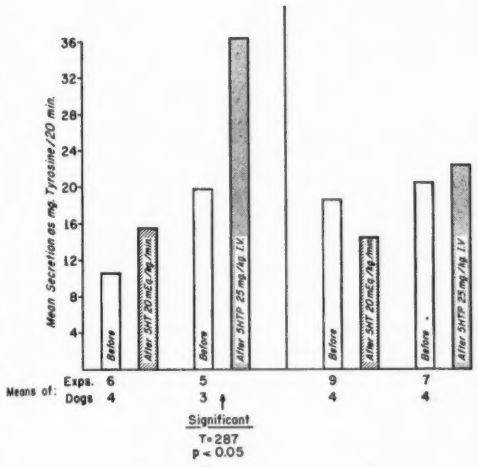
FIG. 2. Effect of 5HTP and 5HT on fundic pouch dogs given histamine every 10 minutes. There is no clear change in the rate of water or acid secretion in either Pavlov or Heidenhain pouches stimulated with large or small doses of histamine with 5HT or 5HTP.

DISCUSSION

Since 5HT is known to exist in a tissue-bound form in the gastrointestinal tract, it was difficult to assess its role by administering intravenous free 5HT in the normal dog. We have attempted to solve this problem by giving 5HTP which is the physiologic precursor of 5HT, and thus determine more closely the physiologic activity of naturally occurring 5HT.

Serotonin appears to cause a drop in food stimulated acid secretion in innervated Pavlov pouches with changes in volume and acidity partially due to decrease in secretion of water and hydrochloric acid, and partially due to mucin production. Serotonin precursor causes similar changes as previously reported by Haverback, and is accompanied by hypermotility, excitement, and hyperventilation during the period of inhibition. Since the changes in acid and volume occur primarily in Pavlov pouches and only questionably in Heidenhain pouches these must depend on the integrity of parasympathetic innervation. The normal inhibitory mechanisms may be involved in some manner since 5HT produces some inhibition. Complete depletion of the bound 5HT by reserpine is followed by prolonged hypersecretion, with perforation of an ulcer and death in 1 dog.

Further experiments with histamine stimulated dogs showed a trend in the same direction as in the food stimulated dogs although this observation could not be considered significant. This is completely contrary to the findings of European investigators who found clear inhibition of histamine stimulated secretion using anesthetized dogs after total gastric fistula and pylorus ligation. We can only infer from the difference in type of preparation that antral inhibition played a larger part in these dogs than ours. The clear increase in pepsin production in both short term experiments is again in Pavlov and not in Heiden-



a FIG. 3. b

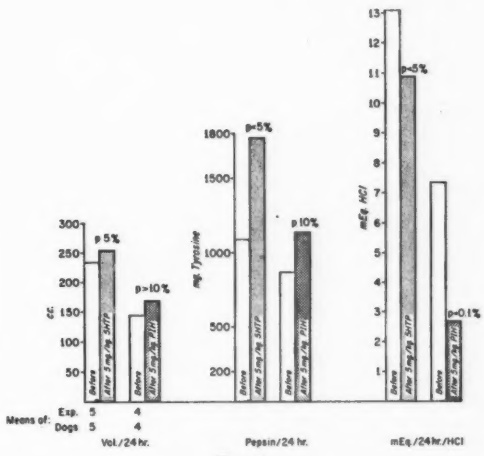


FIG. 4.

FIG. 3. Effect of 5HTP and 5HT on histamine stimulated pepsin secretions of fundic pouches. a, A clear increase in pepsin secretion is noted in short term experiments on Pavlov pouch dogs using 5HT or 5HTP while, b, this change is not noted in Heidenhain pouches.

FIG. 4. Changes in 24 hour gastric pouch secretions after 5HTP or PIH. A clear increase in volume and pepsin secretion and a drop in total acid production is noted in 24 hour collections in both Pavlov and Heidenhain pouch dogs.

hain pouches suggesting again that this effect is vagally mediated. In 24 hour collections, the rise in pepsin was as clear in Heidenhain as in Pavlov pouches. This finding appears in keeping with the delayed rise in pepsin secretion following feeding noted by Schofield as opposed to the immediate rise found in Pavlov pouches by the same author. Of the several factors important in the production of peptic ulceration, hypersecretion of acid is most generally accepted as a cause. The others are less clear cut. Gastric mucin is important, and is known to be reduced by ulcerogenic drugs. Mucin is increased by 5HT or 5HTP both in the pylorus and fundus. 5HT is the only substance thought to produce mucin by a direct effect on the mucosa and not secondary to motility and rubbing together of the mucosal surfaces. Serotonin may thus have a protective effect in this manner as well as by reduction of acid production. Less clear and a unique observation to these experiments is the increased pepsin production in response to 5HT and 5HTP. This trend occurs clearly both in the short experiments with these drugs and histamine and in the 24 hour collections. A few experiments on food stimulated secretion showed a rise in pepsin as well.

This investigation was conducted because it was discovered that there were large amounts of 5HT in the pyloric mucosa which necessitated the re-evaluation of the role of the pylorus in acid and pepsin regulation and, therefore, the surgical importance, since any factor influencing acid and pepsin is immediately of immense surgical concern. We believe that it probably is inhibitory of acid production, but its effect on pepsin is contrary.

SUMMARY

1. At high rates of secretion in Pavlov pouches, 5HT and 5HTP reduce volume and acid.

2. Neither drug had a significant effect on histamine stimulated volume and acid production in either of the pouches, but increased pepsin in Pavlov pouches.

3. Twenty-four hour collections in both types of preparation show that 5HTP and

the monamine oxidase inhibitor (PIH) decreased acid, increased volume, and increased pepsin significantly.

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THE PHYSIOLOGIC RESPONSE TO THE ILEAL BLADDER

JAMES R. JUDE, M.D., Baltimore, Maryland,

ALVIN H. HARRIS, M.D., and ROBERT R. SMITH, M.D., Bethesda, Maryland

RADICAL RESECTION of pelvic organs for cure or palliation of cancer has necessitated permanent diversion of the urinary stream. Other abnormalities of the bladder including exstrophy, intractable vesicovaginal fistula, contracture, trauma to bladder and ureters, and acquired conditions may likewise require temporary or permanent urinary diversion.

Urinary diversion has been accomplished via nephrostomy, cutaneous ureterostomy, and ureterosigmoidostomy. The necessity for an anatomic method of urinary diversion without alteration of body physiology has prompted the use of these various methods. In order more nearly to achieve this goal the method of urinary diversion to a conduit of ileum, as originated by Shoemaker in 1906 and popularized by Bricker since 1950 (1), is the present method of choice.

A study of the physiologic response of the body to the presence of an external urinary conduit or ileal bladder is presented in this report.

MATERIAL

Twenty-two patients with ileal bladders have been observed for from 6 months to over 2 years following their surgery. In 14 patients the ileal bladder was constructed in the treatment of far advanced carcinoma of the cervix, as a portion of pelvic exenterative surgery. Seven patients with carcinoma of the urinary bladder had urinary diversion via an ileal bladder as an adjunctive procedure to intensive high voltage irradiation of the cancer. A single patient underwent temporary ileal bladder urinary diversion to allow transvesical closure of a large ureterovesicovaginal fistula.

The method of creation of the ileal bladder was similar to that of Bricker (1, 2) and has been previously reported (4). The ileal segment was 20 to 25 centimeters in length and the ureteroileal anastomosis performed in two layer mucosa-to-mucosa, end-to-side fashion. A nonobstructing ileostomy opening was made in the right lower quadrant of the abdomen. Free urine flow at all times occurred into a disposable plastic bag which adhered to the skin.

These patients were examined frequently with serial intravenous and retrograde pyelograms, hemograms, serum electrolytes, and renal function studies. Follow-up intervals were monthly, for the most part, following operation and discharge from the hospital. No patient was lost to follow-up.

RESULTS

In Table I are shown the results of excretory pyelography studies in terms of individual renal units. It is of interest that 5 renal units with no excretory function preoperatively developed the capacity to excrete dye after anastomosis to the ileal bladder. In line with this it also can be seen that 50 per cent of the renal units when first examined revealed evidence of functional impairment. Subsequently there was a marked shift toward improvement over the first 6 months postoperatively, and often by 3 months. In the immediate postoperative pyelograms a rather uniform but transient decrease in function was noted as seen in mild to moderate degrees of dilatation of the ureter and pelvic area of the kidneys. Again, by 3 months these changes had all reverted toward normal.

From the Surgery Branch, National Cancer Institute, National Institutes of Health, Public Health Service, United States Department of Health, Education, and Welfare.

TABLE I.—INTRAVENOUS PYELOGRAPHIC RENAL FUNCTION IN 22 PATIENTS

	Total No. renal units studied	*Per cent in each division‡*				
		N±	*Mi±*	*Mo±*	*Ma±*	*O±*
Preoperative	45*	55.5	11.1	9.0	6.7	17.7
6 to 24 months	45*	75.4	9.0	9.0	0.0	6.6†

*One kidney unit surgically absent; includes 2 double kidney units.
†One nonfunctioning kidney unit of long duration not anastomosed to ileum; the other 2 units also had no function preoperatively.
‡N=normal, Mi=minimal hydronephrosis, Mo=moderate hydronephrosis, Ma=marked hydronephrosis, O=no radiographic function.

The status of renal function was further studied by phenolsulfonphthalein excretion, serum creatinines, and blood urea nitrogens as shown in Table II. The great majority of cases demonstrate values within the normal range. The sole abnormal values are found in those patients who were noted to have had chronic pyelonephritis associated with ureteral obstruction prior to formation of the ileal bladder. There was no instance of increasing abnormal values in these parameters when compared to the preoperative determinations.

Serum electrolytes were periodically studied in all patients (Table III). Nine patients had carbon dioxide combining powers below the normal range in our laboratory with 4 of the patients having had known chronic pyelonephritis preoperatively. Four patients were noted to have slightly elevated levels of serum chloride in the early postoperative period, but only 1 persistently elevated value could be demonstrated in the long term follow-up. Again, this was in a patient with chronic pyelonephritis prior to surgery. As is expected with only slight aberrations, no clinical symptoms could be traced to abnormal chemistry findings. Repeated determinations of the white blood count, differential count, and hematocrit failed to reveal any alterations from the normal.

TABLE II.—RENAL FUNCTION AT 6 TO 24 MONTHS

	Studied No.	*Normal No.*	*Per cent*
PSP excretion (>55 per cent in 2 hrs.)	16	15*	94
Creatinine (0.6 to 1.1 mgm. per cent)	13	11*	85
BUN (8 to 22 mgm. per cent)	22	20*	91

*Abnormal values: a) 40 per cent excretion PSP in 2 hrs.
b) 1.2, 1.3 mgm. per cent creatinine and
c) 27, 29 mgm. per cent BUN
All with abnormal values had chronic pyelonephritis preileal bladder formation.

Urine collected from the ileal bladder via a sterile catheter was cultured in all 22 patients. On occasion it was found to be sterile but usually contained one or more of the following organisms: Proteus mirabilis in 8 cases, Escherichia coli in 7, Streptococcus group D in 5, Paracolon aerogenes in 5, pseudomonas in 3, klebsiella in 3, diphtheroids in 3, salmonella in 2, and Staphylococcus albus in 2 cases. The colony counts ranged from 1,000 to as many as 1,000,000 per milliliter. The results of the cultures bore no relationship to clinical infection for all patients were asymptomatic when the cultures were obtained.

Urinalyses of ileal bladder urine revealed adequate concentrating ability, absence of glucose, occasional traces of protein, and large quantities of mucus and white cells.

Retrograde radiographic studies of the ileal bladder were performed in 15 patients with the following results: bilateral ureteral regurgitation in 9 (60 per cent); unilateral ureteral regurgitation in 4 (27 per cent); and no ureteral regurgitation in 2 patients (13 per cent). The upper urinary tract and bladder usually expelled the radiopaque dye in a few minutes and the bladder was always found empty in the 15 minute film. Fortuitous valve-like action at the ureteroileal anastomosis in the absence of anatomic obstruction was not unusual. Eight ureters could not be filled by retrograde injection of the radiopaque dye. However, only 1 of these was actually anatomically obstructed as shown by intravenous pyelography.

Spontaneous attacks of pyelonephritis in the absence of obstruction to the outflow of urine were not observed during the entire study period. Chronic pyelonpehritis persisted in those cases in which it was present before surgery, but did not progress. The general condition of all patients remained excellent unless their cancer recurred. Eight patients have expired. One died of a staphylococcal pneumonia 1 month after surgery,

and in the other 7, death was a direct result of the cancer. In all but 1 case the ileal bladder continued to function well. In the sole exception death was due to a recurrent cervical cancer which grew into the ileal bladder, obstructing both ureters.

TABLE III.—SERUM ELECTROLYTES AT 6 TO 24 MONTHS

		Studied	*Preop. normal*	*Postop.* normal*
CO_2	(27 to 33 mEq./L.)	22	18	13
Cl	(99 to 110 mEq./L.)	22	20	21
Na	(136 to 146 mEq./L.)	22	21	21
K	(3.5 to 5.5 mEq./L.)	22	21	21

*Abnormal CO_2 21–26 mEq./L. (4 with chronic pyelonephritis present preoperatively.
Cl 124 mEq./L. associated preoperative chronic pyelonephritis.
Na 152 mEq./L. associated preoperative chronic pyelonephritis.
K 2.8 mEq./L. associated preoperative chronic pyelonephritis.

DISCUSSION

The danger to the upper urinary tract by recurrent infection has been a primary objection to the use of nephrostomy, cutaneous ureterostomy, and ureterocolic anastomosis. This latter procedure has been noted to carry not only a high incidence of ascending infection but also frequent obstruction and electrolyte abnormalities, consisting of a hyperchloremic acidosis and low serum potassium. These complications encouraged the search for other methods of diverting the urinary stream, thereby prompting the trials with an ileal conduit which have proved quite successful.

As can be seen from the follow-up studies, kidney function in the patients presented either remained good or improved as measured by excretory pyelography, phenosulfonphthalein excretion, serum creatinines, blood urea nitrogens, and the concentrating ability of the kidneys. Studies of serum electrolyte values have also failed to show significant abnormalities. The slightly lowered levels of carbon dioxide in the absence of hyperchloremia require continued follow-up study. It is possible that long term studies will show other abnormalities.

A simple, easily created anatomic urinary diversion is essential in the management of the problems created by pelvic exenterative surgery. The ileal conduit bladder appears to fulfill many of the needs. Unanimity has been lacking, however, on the positive value of the ileal bladder. Cases of hyperchloremic acidosis and acute pyelonephritis have been reported. Eiseman and Bricker have shown (3) that both chloride and urea in normal urine concentration are absorbed from an ileal segment in the human. They suggested that the finding of abnormal blood values depended in part on the concentration of the substance in the urine, the length of time the urine remained in contact with the absorbing surface of the intestinal tract, and the area of intestinal mucosa exposed to the urine. Lapides believed that the cause of hyperchloremic acidosis in ureterosigmoid anastomoses was an imbalance of absorption and excretion. It was believed that the presence of diseased renal units contributed to the abnormalities noted and that with normally functioning kidneys, abnormal blood electrolytes did not occur. These ideas would appear to be borne out in this present study.

Bacteriologic study in these patients has revealed the almost constant presence of a variety of organisms in the ileal bladder urine. Acute pyelonephritis is associated with bacteria reaching the upper urinary tract. In this study even in the uniform presence of bacteria in the ileal bladder and a majority of patients demonstrating free ureteral reflux on retrograde studies, overt acute pyelonephritis was not noted in the absence of definite obstruction to the outflow of urine. In fact, there was only 1 episode of acute infection in the entire series, and this was associated with temporary inadvertent obstruction at the ileostomy stoma. This patient responded well to the routine therapeutic measures.

The ileal segment forms a buffer between the outside environment and the sensitive upper urinary tract. Active peristalsis in the loop is constantly present which tends to keep the segment in a nearly empty state as well as discouraging the retrograde invasion of pathogenic organisms via the loop and

ureters to the kidneys. The well constructed, nonobstructing ileal segment provides therefore, a protective mechanism against bacteria as well as a rapidly emptying small surface area for electrolyte absorption. The absence of infection in preserving normal renal function provides a further safeguard against the development of marked acidosis and electrolyte abnormalities. For these reasons it would appear that the ileal bladder maintains normal body mechanisms to a greater degree than other methods of urinary diversion which have been employed in the past.

SUMMARY AND CONCLUSIONS

Twenty-two patients were subjected to the creation of an ileal bladder in the process of therapy of pelvic carcinoma. Serial studies have been performed in order to evaluate the effect of this method of urinary diversion on the physiologic mechanisms of the body. The follow-up periods of study ranged from 6 months to over 2 years following the formation of the ileal bladder. These studies revealed that in this period these physiologic mechanisms were not adversely affected. Renal function was maintained or improved, blood electrolytes were not abnormally altered, and the upper urinary tract was not damaged by ascending infection.

The ileal bladder has proved to be a valuable method of temporary or permanent urinary diversion.

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THE USE OF CLOSTRIDIUM HISTOLYTICUM ENZYMES IN THE TREATMENT OF EXPERIMENTAL THIRD DEGREE BURNS

EDWARD L. HOWES, M.D., INES MANDL, Ph.D., STEPHEN ZAFFUTO, B.S., and WOLFGANG ACKERMANN, M.D., New York, New York

Two enzyme preparations described previously (2, 7, 8) have been made from Clostridium histolyticum filtrates: an ammonium sulfate precipitate (A) rich in collagenolytic in addition to its proteolytic activities, and a methanol precipitate (M) containing only traces of collagenase, some peptidases, and as its main constituent a cysteine inhibited proteinase. Each alone and combinations of each have been tested in vitro for their capacities to digest burn slough, and (A) has been used to remove slough from experimental third degree burns in animals when applied by various methods. Included are data on the substrates that (A) will attack and in vitro studies about substances that inhibit its enzymatic activity.

IN VITRO TESTING OF ENZYMES

To estimate the relative capacities of (A) and (M) and of mixtures of both to digest burned skin in vitro, the following technique was employed. Burns were made on either side of the back of a shaved rabbit with an electric cautery (1 by 0.5 cm.), developing 250 degrees F. in 5 minutes of light contact with the skin. This method, long employed by Howes and Ackermann (4), produced a rather constant third degree burn approximately 1.3 centimeters in diameter consisting of a small charred central area surrounded by a circular zone burned to a lesser degree (Fig. 1). At the center, this burn penetrated down through the deep fascia. After 24 hours the partially burned zone swelled and became demarcated from the surrounding healthy skin by a pink erythematous circumference. At this time the burn was excised above this circumference.

For the test, the burn button was cut out with deep fascia when adherent after washing the surface with a mixture of streptomycin and sulfamylon. At removal the button was always thicker than the surrounding skin. After again immersing it for 10 minutes in the same antibacterial solution, the button was placed in a sterile tube containing 7 milliliters of the enzyme solution to be investigated; made up on the basis of azocoll-collagenase activity.[1] The tubes were incubated at 37 degrees C. and read for digestion after 18 and 24 hours.

What the enzymes must digest could be seen on microscopic examination. The charred center had no particular anatomy nor staining characteristics. The rim or outer zone was found to be composed of deformed and browned collagen fibers that took stains poorly. Only a rare leucocyte was seen between these fibers and no blood vessels were visible. Its surface consisted of a condensed layer with no identifiable epithelium or keratin (Fig. 2).

After each test, the solutions were examined for the presence of bacteria and for

From the Departments of Surgery, Biochemistry, and Microbiology, College of Physicians and Surgeons, Columbia University, New York.

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[1]Azocoll or Q units = proteolytic activity = capacity to digest denatured collagen.
Collagenase units = ninhydrin units = capacity to digest undenatured collagen.

TABLE I.—RESULTS OF IN VITRO TESTS OF (A) AND (M)

(A) 265		(M) 224		Total		Digestion at 24 hours	
Azocoll	*Collagenase*	*Azocoll*	*Collagenase*	*Azocoll*	*Collagenase*	*Center*	*Rim*
250	138	0	0	250	138	4+	+
250	138	0	0	250	138	4+	+
500	276	0	0	500	276	4+	2+
500	276	0	0	500	276	4+	2+
3000	1640	0	0	3000	1640	4+	4+
3000	1640	0	0	3000	1640	4+	4+
0	0	3000	230	3000	230	4+	2+
0	0	3000	230	3000	230	4+	2+
0	0	5000	384	5000	384	4+	2+
0	0	5000	384	5000	384	4+	2+
0	0	6000	460	6000	460	4+	3+
100	55	2900	222	3000	277	4+	3+
100	55	2900	22	3000	277	4+	3+
250	138	1750	134	2000	272	4+	4+
250	138	1750	134	2000	272	4+	4+
500	138	2500	192	3000	468	4+	4+
500	138	2500	192	3000	468	4+	4+
100	55	2900	222	3000	277	4+	2+
			Phosphate buffer				
100	55	2900	222	3000	277	4+	4+
			Calcium borate				
500←15 min. (then 3000 for 24 hours)						4+	2+
Tryptar	—	—		300	—	+1	0

At 4+ digestion the tissue went into solution or became an amorphous jelly; with 2+ the tissue was thinned but still intact.

changes in hydrogen ion concentration. When bacteria were present or if the *p*H had changed markedly the results were discarded even though the discovery was made that, unlike trypsin, these enzymes did not seem to be readily destroyed in the presence of bacteria.

The results are shown in Table I. The charred center was readily digested by even the smallest amounts of (M) or (A) and by trypsin, indicating that it was composed of completely denatured collagen. By contrast, the rim was more resistant to digestion. For example, 500 azocoll units of (A) with 276 collagenase units made only a 2+ attack on the rim, while 3,000 Q units of (M) with 230 collagenase units gave the same results. Three thousand Q units of (A) with 1,640 collagenase units completely digested the rim, while with 6,000 Q units of (M) with 460 collagenase units, the attack was still only 3+. The combination of (M) and (A) seemed to be more powerful in digesting the rim than either alone because 250 Q units of (A) with 1,750 Q units of (M), total Q 2,000 units, and collagenase 272 units completely digested the rim.

After skin was digested, the remaining debris consisted of keratin, hair, epithelium, and elastic fibers. When tissues other than skin were incubated in (A) in vitro those composed of collagen or having a collagen component were attacked. (A) also attacked tendon, cartilage, fascia, ligaments, and loose connective tissues and removed the connective tissue stroma from muscle, leaving a pink mass of myosin behind. Fresh bone was only weakly attacked at its periphery by a strong solution of (A) containing 7,400 collagenase units per milliliter, but when the salts were removed from the bone by EDTA the remaining collagen structure was quickly liquefied by an (A) solution containing 2,460 collagenase units per milliliter. On the other hand, finely ground bone salts did not interfere with the digestion of collagen. Thus, the presumption must be made that the inorganic constituent of the bone prevented the enzyme from reaching the collagen fibers. The activity of (A) was cut down slightly in the presence of normal rabbit and horse serums. Neither (A) nor (M) attacked fat, fibrin[2], keratin, or elastin. Furthermore, (A) only partially attacked mucoproteins.

[2]On second fractionation of (A) some slight fibrinolytic activity becomes concentrated in the fractions precipitated at 22 per cent ammonium sulfate concentration.

In general, epithelium has been found to be somewhat resistant to attack by (A) both in vitro and in vivo. Recalling that all soft tissue of the leg disappeared rapidly in the experimental animal with clostridial infection, (A) was tried against 755 epithelial tumors in mice shortly after it was first isolated in quantity in 1953. Massive hemorrhage resulted, but the epithelial cells remained. Squamous epithelial cells were found to proliferate at a high level of collagenase activity. For example, the skin of rabbit was immersed in 10 milliliters of 0.5 per cent (A)303 in a streptomycin sulfamylon solution for 4 hours until the tissue became jelly-like and it was then grafted on denuded ears of the same and other rabbits. All grafts took, appearing as a thin layer of epithelium which thickened later, but the homologous ones were absorbed again, indicating that the antigenicity must be toward the epithelial cells and not their stroma while the autogenous ones remained. Also, we dressed daily ear wounds of rabbits beginning the fourth day after wounding when granulations had appeared, with amerchol H9[3] containing 1 milligram per gram of (A)303. The granulations continued in good state and the rate of epithelization was average. On the other hand, as would be expected, the tissues of fresh wounds were damaged when dressed with this same ointment. Weak solutions of (A) have been used in vitro also to remove surrounding connective tissues to obtain the shape of compound racemose glands. Lesfarges and Pomerat have used (A) in very dilute solutions to dissolve connective fibers from tissue cultures to allow epithelial cells to grow. The only evidence we have that certain types of epithelium might be more sensitive to (A) was obtained by Roberts working in our laboratory who found that epithelium from the stomach mucosa of the rat immersed in 1 milligram per milliliter of (A)268 for 15 minutes did not transplant but when put in 0.1 milligram per milliliter for 4 hours it took. Finally, Prudden found that 0.5 milligram per 5 milliliters of (A) given intraperitoneally to the rat under anesthesia caused intense destruction of the posterior parietal peritoneum. Two weeks later the posterior muscles were still exposed. There were few adhesions and no destruction of the intestines. The anterior peritoneum had not been destroyed, suggesting that the enzyme fixed rapidly and destroyed the posterior area. This apparent susceptibility of mesothelial cells can perhaps be associated with the occurrence of pulmonary hemorrhages after the intravenous administration of (A) in toxicity tests when the endothelial linings of capillaries of the lung were destroyed.

[3]A cholesterized petrolatum.

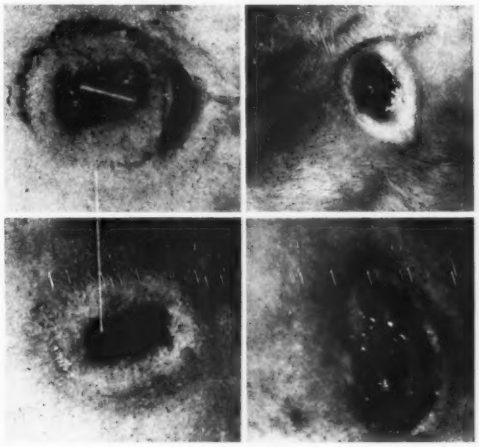

FIG. 1. Lower left, Gross appearance of "button" 24 hours after burning. Charred center is rectangular and has the shape of the instrument used to make the burn. Whiter circle is less denatured third degree burn. Upper left, Burn button separating around the periphery. Aluminum marker, 1 centimeter long, in the charred center. Lower right, Appearance of the base at the time of separation. Granulations in good condition. Upper right, Burn button healing.

EXPERIMENTAL BURNS IN RABBITS

Experimental third degree burns were made in the skin of rabbits by the method just described. One to 3 were placed on either flank. Rabbits 4 months old of approximately 2.5 kilograms were used. Initially, those of any color were employed but as the work progressed it became evident

TABLE II.—SEPARATION OF 3 DAY BURNS IN RABBITS WITH INJECTIONS OF (A)

	Collagenase activity
A 303	
1 mgm./ml. 2 off 24 hrs. Hemorrhage	610
0.5 mgm./ml. 1 not off 48 hrs. Hemorrhage	310
0.384 mgm./ml 2 off 48 hrs. Very slight hemorrhage	230
0.192 mgm./ml. 2 off 24 hrs. Very slight hemorrhage	115
0.096 mgm/ml. 2 off 48 hrs. No hemorrhage	58
.048 mgm./ml. 1 off 48 hrs. 1 off 24 hrs. No hemorrhage	29
.024 mgm./ml. 1 off 48 hrs. 1 off 24 hrs. No hemorrhage	15
.012 mgm./ml. 2 not off	7.5
.006 mgm./ml. 2 not off	3.8
A264	
.096 mgm./ml. 1 not off 48 hrs. Slight hemorrhage	240
.048 mgm./ml. 1 off 24 hrs. 1 off 48 hrs. Slight hemorrhage Buttons ¾ digested	120
.024 mgm./ml. 2 off 24 hrs. Very slight hemorrhage Button ½ digested	60
.012 mgm./ml. 3 off 24 hrs. No hemorrhage Button thinned	30
.006 mgm./ml. 2 off 24 hrs. No hemorrhage	15
.003 mgm./ml. 1 off 1 not off	7.5
.0015 mgm./ml. 2 not off	3.8

that albinos were more suitable because their skins developed a reactive dermatitis with minimal insult, a circumstance similar to those found in humans. The treatment of the burns with enzymes was usually started immediately after burning unless otherwise indicated. Three methods of application were employed: by injection, wet dressings, and ointments.

When the button separated, its condition and that of the base was observed: whether it was intact, thinned, or partially or completely digested. Depth of separation, whether down to the muscle or superficial, was recorded. The base exposed beneath was inspected to ascertain if the blood supply was uninjured, or whether there was necrosis. Occasionally the tissues of the base appeared healthy but sloughing began again. When untreated in any way the button dried and sloughed in about 2 weeks leaving healthy granulations beneath (Fig. 1). The button separated intact and was as thick as the surrounding skin. Microscopically the line of separation of slough occurred central to the collection of leucocytes that infiltrated the unburned tissue just beyond the pink circumferential ring previously described. Hence they were thought to be the source of the natural enzymes that separates slough (Fig. 2). After separation, contraction and epithelization took place, and about another 2 weeks' period was usually required for complete healing.

SEPARATION WITH INJECTION OF ENZYMES

With a daily injection of 1 milliliter of distilled water or saline beneath, the buttons usually sloughed in 9 or 10 days. Sometimes the edges partially separated after 3 days but not the base. Separation of the base with its perpendicular strands of unburned connective tissues required 10 days. When separated, the buttons were thicker than the surrounding skin. At first the enzymes were injected in 2 ways, beneath in some and into the buttons in others. With injection into the button the effect of the enzyme on the surrounding tissues was difficult to judge. Therefore, in these experiments the amount of enzyme dissolved in 1 milliliter of water was injected beneath the burn.

Different amounts of (A)303 and (A)264 were required to remove burn buttons by injection. (A)303 produced by H_4 strain

Clostridium histolyticum is the least toxic of the (A) enzymes tested and contained about 610 collagenase and 6,500 Q units per milligram of powder while (A)264 produced by 230-2 strain contained approximately 2,400 collagenase and 4,500 Q units per milligram.

Also, different results were obtained when the button was injected immediately after burning and 3 days later. Immediately after burning, all buttons injected with 1 milligram per milliliter of (A)303 containing 610 collagenase and 6,500 Q units separated in 24 hours and had hemorrhage beneath. With 0.5 milligram per milliliter only about half of the burns separated and there was less hemorrhage beneath, while with 0.25 milligram per milliliter containing 152 collagenase and 1,625 Q units there was a very small amount of hemorrhage but only about 30 per cent separated after 24 hours. All separated at 48 hours. With (A)264 injected immediately after burning, as little as .07 milligram per milliliter containing 172 collagenase and 315 Q units removed buttons in 24 hours and there was still a small amount of hemorrhage beneath.

Table II shows that considerably smaller amounts of enzymes were required when the injections were made 3 days postburn. With (A)303, as little as .096 milligram per milliliter with 58 collagenase and 624 Q units removed the buttons in 48 hours with no hemorrhage beneath. All greater concentrations while removing slough in 24 hours caused some hemorrhage although the amount with 0.192 milligram per milliliter containing 115 collagenase and 750 Q units was very small. In the opposite direction down to .024 milligram per milliliter with 15 collagenase and 157 Q units removed 50 per cent of the sloughs without causing hemorrhage. Less than .012 milligram per milliliter containing 7.5 collagenase and 78 Q units did not remove slough.

With (A)264, .012 milligram per milliliter with 30 collagenase and 54 Q units removed buttons in 24 hours, and there was no hemorrhage beneath. The next dilution

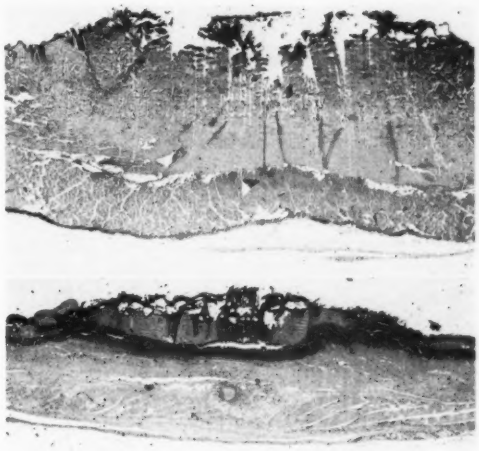

FIG. 2. Upper, Skin immediately after burning. Loss of anatomic structures in charred center seen on either side; central area thickened. Lower, Burned skin at 8 days; central area still slightly thicker. Slough on surface with a long dense row of leucocytes beneath. In the depths of the central area is an engorged lymph channel filled with edematous fluid.

.006 milligram per milliliter with 15 collagenase and 27 Q units also removed all sloughs without producing hemorrhage. The next dilution did not remove slough. The lowest concentration producing hemorrhage (slight) and removing slough was .024 milligram per milliliter containing 60 collagenase and 108 Q units.

In summary then, although smaller amounts were required at the later period, about one-eighth as much of (A)264 as of (A)303 was required to remove slough at either time and this difference was explained by the collagenase and not the azocoll activities of each preparation. (A)303 removed burn slough without producing hemorrhage from 58 down to 15 collagenase units and with 624 down to 157 Q units. (A)264 did likewise from 60 down to 15 collagenase units and with only 54 down to 27 Q units. Interestingly both lost their capacity to remove slough at the same collagenase activity, i.e., 15 units.

It will be recalled that in fresh tissues more than 3.8 collagenase units of (A)264 or (A)303 were required to produce hemor-

TABLE III.—RESULTS OF INJECTION OF (M) BENEATH BURN IN RABBITS

Q units	*Collagenase*	*Day of injection*	*Day of separation*	*Hemorrhage*	*Condition of button*	*Condition of base*
500	60	Immediately	3	0	Intact	Superficial
750	94	Immediately	3	0	Intact	Superficial
1000	124	Immediately	3	0	Intact	Superficial
1500	188	Immediately	3	0	Intact	Superficial
2000	250	Immediately	3	0	Intact	To muscle
3000	380	Immediately	3	0	Intact	To muscle
600	760	Immediately	3	0	Intact	To muscle
1000	124	3	4	0	Intact	To muscle
1500	188	3	4	0	Intact	To muscle
2000	250	3	4	0	Intact	To muscle
3000	380	3	4	0	Intact	To muscle
4000	500	3	4	0	Intact	To muscle
6000	760	3	4	0	Intact	To muscle
1000	124	4	5	0	Intact	Includes muscle
1500	188	4	5	0	Intact	Includes muscle
2000	250	4	5	0	Intact	Includes muscle
3000	380	4	5	0	Intact	Includes muscle
4000	500	4	5	0	Intact	Includes muscle
6000	760	4	5	0	Intact	Includes muscle
6000	1580	2	3	—	Half digested	Some hemorrhage
6000	125	2	5	0	Intact	Clean

Collagenase determinations are only approximate. Original determinations when low are difficult to obtain accurately and errors are multiplied when compiling total units.

rhage. On the other hand, immediately after burning, 29 collagenase units of (A)303 or more were needed to produce hemorrhage while with (A)264, 39 collagenase units were required. Three days after burning 115 collagenase units or more were needed to produce hemorrhage with (A)303, while with (A)264, 60 collagenase units or more were required. Four times as much of (A)303 was needed to produce hemorrhage after 3 days but only 1.6 times as much of (A)264.

Indeed, in 2 rabbits with burns 10 days old and allowed to dry to a hard eschar, 200 collagenase units of (A)303 in 1 milliliter of distilled water injected beneath removed a thin slough in 2 days and left tissues that looked somewhat gray. There were buds of new granulations present but no hemorrhage. This capacity of granulations to resist the action of collagenase will be referred to again when wet dressings are discussed.

When and how buttons separated with 500 to 6,000 Q units of (M) in 1 milliliter of distilled water injected beneath depended also on the collagenase content of the (M) employed (Table III). At 500 Q units or less and 60 collagenase units, separation was either superficial or required 3 days. With 2,000 Q units with collagenase 250 or more, separation was deeper and the button was removed within 24 hours when injected on the third or fourth day after burning. It separated intact and there was seldom hemorrhage beneath although it must be remembered that the enzyme was not injected until late. The role of collagenase contents of (M) can be seen in the last 2 tests in Table III. Both buttons were injected beneath on the second postburn day with 6,000 Q units of (M). One (M) contained 1,580 units of collagenase while the other contained 125 units. With the first the button was off in 24 hours, half digested, and there was hemorrhage beneath. With the second, 3 days were required; the button came away intact, was thick, and there was no hemorrhage beneath.

In general, therefore, any advantage that (M) enzyme may have as compared to (A) for injection depends on its smaller content of collagenase, equivalent to a weak (A)303 solution.

Although the injection of these enzymes in the proper concentrations removed slough experimentally, these results should not be interpreted as recommendation of injection of these enzymes for the clinical

treatment of burns or sloughing lesions. However, one of us (Howes) has used (A)303 properly diluted to remove sloughing tendons in diabetic gangrene and to remove fascia in bed sores. Placed in the specific structure by means of a fine hypodermic needle these masses of undenatured collagen were quickly gelatinized without causing hemorrhage. It has been reported also (5) that a fraction precipitated between 30 and 35 per cent ammonium sulfate concentration rich in peptidase and containing a small amount of collagenase is the best preparation for injection.

Certainly, for old and leathery eschars, injection places the enzymes where they can be effective. We have also put these enzymes below eschars by means of the hypospray. It was feared that the enormous pressure used to propel the solution might destroy the enzyme, but the slough came away in 24 hours, and no hemorrhage resulted.

SEPARATION OF SLOUGH BY WET DRESSINGS

Before describing the experimental application of (A) and (M) to burns by means of wet dressings, their stability in solution and conditions inhibiting their action must be considered. Some aspects of this problem have been presented previously (8).

To be successful in wet dressings, enzymes must retain their activity. The stability of solutions of (A) as judged by in vitro tests was found to vary with *p*H, concentration, and ions present; 0.1 per cent solutions of (A) in water, in saline, phosphate saline buffer or calcium borate buffer retained full activity after 1 month at 4 degrees C. At room temperature all activity was lost after 96 hours in phosphate buffer while 25 per cent was lost after 24 hours. In calcium borate buffer, in saline, and especially in distilled water, stability was maintained longer at room temperature. Some calcium ions are necessary for the activity of (A) but an excessive amount does not enhance it (Table IV).

Heating to 56 degrees C. for 30 minutes destroyed all collagenase and most azocoll activity. Preparations used clinically then must be sterilized by filtration. (A) has no bacteriostatic properties, in fact, being protein it may support growth of bacteria.

(A) and (M) are compatible with each other, but when mixed with various other proteolytic enzymes, collagenase activity was rapidly destroyed. Ablondi has shown that the Clostridium histolyticum enzymes do not autodigest as rapidly as trypsin. Lipase did not interfere with collagenase activity nor vice versa. In the dry state (A) retained its activity for several years but unitage per milligram did decrease with the absorption of moisture. The common enzyme poisons, for example, the mercurial antiseptics inhibited both the azocoll and collagenase activities. Hexachlorophene not only diminished both activities but "tanned" the

TABLE IV.—EFFECT OF SOME METAL IONS AND INHIBITORS ON COLLAGENASE ACTIVITY

Inhibition	*No effect*
Hg 0.2×10^{-3}M or more	Co 0.2×10^{-2}M
Ag 1.6×10^{-3}M (not 0.2×10^{-3}M)	Mg 0.2×10^{-2}M
Cu 0.8×10^{-3}M (not 0.2×10^{-3}M)	Mn 0.3×10^{-2}M
Ni 0.8×10^{-3}M (not 0.2×10^{-3}M)	Ca 0.2 M or less
Zn 0.8×10^{-3}M (not 0.2×10^{-3}M)	Soy trypsin inhibitor
Pb 10^{-3}M (not 0.2×10^{-3}M)	Ovomucoid 0.02%
$Fe^{++}10^{-3}$M	Mucoproteins 0.02%
$Fe^{+++}0.4 \times 10^{-3}$M	Glucosamine 0.02%
Cysteine 0.01M or more	Chondroitin sulfate + Na_2SO_4
*p*Hisohex (2%, 0.2%; slight 0.02% not 0.002%)	Chondrosamine
Triton (2%, 0.2%; slight 0.02% not 0.002%)	Blood group A substance
G-11 3% in propylene glycol 2% not 0.2% (i.e. 0.06% G-11)	Glycerol 0.3%
Versene (Di-Na, Tri-Na or Tetra-Na 4×10^{-4}M	Propylene glycol 0.2%
	Duponol 0.01%
	Stearyl alcohol
	Glyceryl stearate 0.27%
	Parasept 0.0002%
	K hexa & penta thionate 0.1%
	K tetra & penta thionate 0.1%
	Penicillin 30,000 units
	Streptomycin 20 mg
	Terramycin 0.5%
	Aureomycin 0.1%
	Bacitracin 0.5%
	Sulfamylon 0.5%

TABLE V.—DIGESTION OF FRESH HUMAN TENDO ACHILLIS IN VARIOUS OINTMENTS CONTAINING 0.15 MILLIGRAM (A) PER GRAM (CONTROLS WERE ALL X)

	—Time examined—	
	8 hours	*24 hours*
Carbowax (1500)	—	—
Methocellulose	xx	xxxx
Petrolatum	—	—
Petrolatum + lanolin extract (L101)*	—	xxx
Base H9—water—mineral oil *Amerchol L-101 + B square wax (high melting point combination)	—	xxx
Tragacanth jelly	xx	xxxx

Interpretation

Softening of tendon	x
Some fragmentation	xx
Partial destruction	xxx
Complete disappearance	xxxx

*Amerchol L-101 is a liquid multisterol—a nonionic emulsifier and surfactant.

substrate as well making skin treated with G-11 completely resistant to attack. Table IV also lists inhibiting concentrations of other substances.

The optimal *p*H for the activity of (A) was found to be 7.2 but its collagenase activity tended to remain more stable than azocollase toward the alkaline side, remaining efficient between *p*H 8 and 9. Optimum activity ranges of both differed with the buffer used. On the other hand, all the enzymes tested were gradually inactivated toward the acid side and completely inactive below *p*H 5.0. It is helpful to know that the activity of such a powerful enzyme as collagenase can be stopped, if need be, by a weak acid solution but acid conditions can unknowingly be encountered which might partially destroy activity when wanted. For instance, while the antibiotics tested did not inhibit (A) (Table IV) they could be prepared as acid salts which might inhibit. The uninjured mantle of the skin is acid (*p*H 5 to 6) and this, plus the fact that keratin is not attacked by collagenase, suggests that uninjured skin should not be attacked. Because of *p*H also, acids like pyruvic cannot be used to swell collagen before (A) is applied in the treatment of burns. Lastly, certain bacterial infections may set up an acid environment but most, and certainly the well established ones, usually produce an alkaline *p*H. To be certain that an unfavorable environment is not present, the *p*H of the area where the enzyme is to be employed should be measured.

Solutions of (A) were applied by means of fine mesh gauze held on by a plastic patch as suggested by Marion Webster of the Department of Biologic Research, Walter Reed Army Institute of Research. The gauze was wet once daily by means of 1 milliliter of solution put through the small hole in the center of the patch. Five-tenths to 1.5 milligrams per milliliter of (A)303, 305 to 915 collagenase units with 3,250 to 9,750 Q units in distilled water routinely took off and dissolved most of the burn buttons in 48 hours without causing hemorrhage. A slight maceration of the surrounding skin was produced but quickly subsided. (M) solutions also took off the button in 48 hours in concentrations of 2.0 milligrams per milliliter, 6,000 Q units with some collagenase. The attack was made from the surface downward and initially to the charred area. This attack differed from the one obtained when the enzyme was injected beneath the burn and the button separated at its circumference. The absence of hemorrhage with wet dressings was in contrast to the results obtained when the enzymes were injected beneath.

Bacterial growth was enhanced by the use of wet dressings. This was true not only when the button was not digested completely, but even when it was completely removed and the exposed base looked clean. Blood plates smeared from the area grew out solid sheets of staphylococci. When the solution of (A) was made up in 5 per cent streptomycin-sulfamylon solution, neutralized, the button came off in 48 hours and then the smears showed only 1 or 2 colonies of staphylococci. The same reduction in the number of bacteria was obtained repeatedly with 0.5 per cent neomycin and 500 units per milliliter of bacitracin. These results convinced us that wet dressings of (A) should include a noninterfering concentration of an antibiotic.

Howes (3) has previously reported that the combination of an enzyme and an antibiotic reduced the bacterial count of the established infection under certain circumstances while neither alone did so.

SEPARATION WITH OINTMENTS CONTAINING (A)

To be effective, (A) must survive in and diffuse out from the ointments. To investigate these propensities, 1.5 milligrams of (A) was dissolved in a minimal amount of water and then incorporated into 10 grams of ointment base, or only powder was used in grease bases in which no water was accepted. The digestive activity of the mixture was tested at first by placing approximately 5 by 2 by 2 millimeters of fresh rabbit or human tendo achillis in the ointment contained in a Petri dish and incubating at 37 degrees C. It was examined at intervals for fragmentation or actual dissolution. (A) did not act in petrolatum (Table V) but digested tendon when petrolatum contained lanolin extract and some water. A high melting point wax could be incorporated also without disturbing the results. (A) did not act in carbowax 1500 even though water was included. Tendon was also digested when (A) was placed in tragacanth and methocellulose jellies.

These first tests were only qualitative. For quantitative studies, the azocoll plate method previously described was used (8). An aliquot of enzyme-base mixture was placed in a hole of uniform size made in the agar plate. The plate was incubated at 37 degrees C. for 24 hours. Digestion by the enzyme of the dyed hide powder substrate dispersed in the agar resulted in the appearance of a cleared zone around the ointment (Fig. 3). The extent of clearing could be measured. With this method, concentrations of substances other than enzymes that did or did not interfere with activity could be determined together with the influence of the amount of water present. For results in 2 hours, we have used also the photographic film digestion method (gelatin). Ogle and Logan have used quantitative gelatinase

FIG. 3. Azocoll plate. At the top are 2 tubes containing enzyme: that on the left is an ointment; at the bottom is the ointment outside of a tube. Surrounding clear area indicates that collagen particles containing azocoll dye have been digested.

tests for testing clostridial enzyme preparations similar to (A).

For the treatment of experimental burns, the ointment to be tested was spread on fine mesh gauze and applied immediately after the burn was made. The gauze was held in place by means of a circular bandage. If the ointment was of the type that would dry rapidly a sheet of plastic was placed over it to help prevent evaporation. Every 24 hours thereafter, the dressings were removed and the burn was inspected and redressed. The surrounding skin was always observed for dermatitis. Sometimes the ointments were repeatedly put on after slough was removed to ascertain whether additional digestion and necrosis or interference with healing would occur. At other times the enzyme ointment was no longer applied and only the same base containing a small amount of procaine penicillin was used.

The capacity of the ointment to remove slough from the animal could be correlated with its capacity to digest the azocoll plate. For example, (A) in petrolatum failed to remove burn buttons, while in methocel and tragacanth 1 milligram of (A)303 per gram of ointment removed buttons in 24 to 48 hours and did not cause hemorrhage. Slough was removed from the surface downward, a layer at a time with each application. The

charred center was digested in 24 hours. G-11, the mercurial antiseptics, and many of the detergents kept these active ointments from removing buttons, and this inhibition could be demonstrated with the azocoll plate also. Neither streptomycin, sulfamylon, neomycin, nor 10 per cent propylene glycol added to active ointments prevented removal of slough or interfered with azocoll digestion. The tragacanth and methocel jellies tended to dry even with the plastic cover. When dried, the dressing became an extremely hard, inflexible mold.

In the cholesterolized petrolatum, 2 milligrams of (A)303 per gram digested the azocoll plate slightly and removed burn buttons in 3 to 4 days, when water in the ratio of 2 to 1 was added. In 33 per cent of burns treated with this much water in the ointment a mild dermatitis developed. If the amount of water was reduced to 10 per cent, even 4 milligrams of (A)303 per gram did not digest azocoll. This type of ointment has been "shelf tested" and showed good maintenance of enzymatic activity after many weeks at refrigerator temperature. In fact, the incorporated antibiotics which did not interfere with shelf life of the enzymes did not maintain potency for a comparable length of time if the ointment contained over 20 per cent water.

ANTIGENIC PROPERTIES

The enzymes produced by Clostridium histolyticum being proteins should be antigenic. Apart from the remote possibility of a severe allergic reaction the development of inhibiting antibodies against them may not be important unless the enzymes were used repeatedly over a long period of time. Separation of sloughs occurred in rabbits in 48 hours or at a time not sufficiently long for antibody production seriously to interfere with their activity. We actively immunized 2 rabbits intravenously with a solution of (M) high in collagenase. Both rabbits were given a course of injections at weekly intervals and showed considerable antibody production 3 weeks after the last injection. A third rabbit was passively immunized with an intravenous injection of 10 milliliters of an antihistolyticum horse serum, known to have a high anticollagenase and antiproteinase content. This serum was 1 of 6 supplied by C. L. Oakley of Leeds University, England. These animals were then burned and treated with the same (M) which was applied locally in an ointment. In all of these instances, the sloughs separated within 24 to 48 hours. No untoward reactions were observed.

DISCUSSION

The in vitro tests showed that there was a difference in the susceptibility of various portions of the burns to the action of (A) and (M) enzymes. The charred portions were digested by proteolytic components of these enzymes or proteinases similar to trypsin. No collagenase was required for this digestion although it would do so readily if present and the capacity to digest such completely denatured tissue could be estimated by azocoll activity. On the other hand, the less severely burned portions required collagenase for digestion and the degree of attack could be estimated by the number of collagenase units present. Correspondingly, in the application of these two enzymes to the experimental third degree burn in rabbits the (A) enzyme proved best undoubtedly because of the presence of considerable amounts of undenatured collagen in the burn. In the in vitro tests also the (A) enzymes did not attack fat, keratin, fibrin, or muscle and this same specificity was carried over in the treatment of experimental third degree burns.

In the treatment of the burn in the animal, slough was found to become more susceptible to the action of (A) enzymes as the burn became older perhaps because of assistance from naturally occurring enzymes. With the passage of time also, the tissues surrounding the burn and the granulations showed less propensity to hemorrhage when injected with (A) enzyme than fresh tissues. Treatment of the burns with (A) enzymes in

wet dressings or ointments did not cause hemorrhage at any time.

Since collagenase played a dominant role in the removal of slough when (A) was applied to burns, conditions had to be set up in such a way that this enzyme retained its activity. This meant that any medium in which (A) was dissolved, be it solution or ointment, had to have the correct *p*H and be devoid of interfering ions or inhibitors. For the same reason all first aid treatments of the burned area with inhibiting substances generally used to "clean" had to be avoided.

Ointment bases were specifically constructed on the basis of the azocoll plate test to keep the enzyme present as long as possible. With these ointments renewal was less frequently needed. When wet dressings were used, the solutions had to be made as late as possible since stability of the enzymes in the dry state was infinitely greater. Both solutions and ointments kept better when refrigerated. The latter had the longer "shelf life."

No evidence was obtained from these experiments that the burned area was ever made worse by the concentration of (A) enzymes employed. Likewise, healing of the burn was not distorted when (A) enzymes were applied daily until the time when slough was removed. Epithelium and granulations were found to be more resistant to the action of (A) enzymes than burn slough.

The repeated application of (A) enzymes did not change the local bacteriologic flora, nor was there an increased tendency toward infection among the burns treated. If anything, maceration caused by wet dressings of (A) increased the flora as is characteristic of wet dressings in general. Undoubtedly the bacteria were able to survive on the enzymatic degradation products as well as on the originally burned tissues.

The finding that antibiotics can be used with the (A) enzymes without interfering with the action of either is indeed a fortunate one. Experimental burns treated with the combination of each from the beginning had a reduced bacterial flora and of course the length of time when the local condition would support this flora was reduced in duration because the enzymes removed the slough.

Finally it should be pointed out that the amount and concentration of (A) enzymes used in these experiments by any of the methods of application in no way affected the general well-being of the rabbits employed. The concentrations used here were adequate for the treatment of third degree burns in this animal but the results do not mean that this is the proper concentration of (A) enzymes to use in order to remove slough in burns of humans.

SUMMARY

Properties and optimum conditions for application of proteolytic and collagenolytic Clostridium histolyticum enzyme preparations to experimental third degree burns in rabbits are described.

Ammonium sulfate precipitates (A) because of higher collagenase to total proteolytic activity ratios are more powerful in removing burn buttons than methanol precipitates (M). In vitro tests showed collagenase necessary to digest undenatured burned collagen although it attacks the denatured portion of the burn as well. The proteinase components of these enzymes can, like trypsin, attack the denatured portion of the experimental burn.

Three methods were used for application of (A) and (M) enzymes to experimental burns. Each method has advantages and disadvantages.

Injections in aqueous solutions required the least amount of (A) enzyme and placed this amount where it could be most effective. However, collagenase activity had to be diluted to prevent hemorrhage in the treatment of fresh burns. The tissues surrounding older burns and granulations developed some resistance to hemorrhage. Injection removed the burn button from the base upward.

Wet dressings of aqueous solutions did not cause hemorrhage and removed burns from

the surface downward. Control of *p*H and all admixtures was necessary to retain enzyme activity. Specificity of the enzymes and effect of salts and other substances are described. Wet dressings cause maceration and increase the bacterial flora of the burn.

Ointment bases in which enzymes are applied must be chosen to allow diffusion. They must not dry out. The capacities of various ointments to dissolve and remove slough in vitro and in vivo are described. Ointments remove burn slough from the surface downward. Ointments can be prepared in advance for a series of applications to burns.

Antibiotics do not interfere with the action of (A) enzymes and should be used with them to limit growth of bacteria.

Certain types of first aid treatment can render the burn unresponsive to subsequent enzyme therapy and should be avoided.

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BENIGN NEOPLASTIC AND NONNEOPLASTIC DESTRUCTIVE LESIONS IN THE LONG BONES OF THE HAND

ARTHUR H. STEIN, JR., M.D., St. Louis, Missouri

ENCHONDROMA is often the only diagnosis considered when a central destructive lesion of the phalanges of the hand is discovered on roentgenographic examination. Enchondromas are the most frequent tumors to destroy bone in the phalanx of a finger; however, other pathologic entities may also occur in the long bones of the hand. A review of our surgical pathology department files has revealed a group of lesions which show evidence of bone destruction in the phalanges or metacarpals. All of these lesions have been benign. These cases have brought to our attention the fact that several benign lesions occur in the phalanges and metacarpals of the hand with a significant incidence.

Primary malignant tumors and metastatic tumors occur in the hand, but they are relatively rare. Kerwin has reviewed the literature on metastatic tumors of the hand and was able to find only 23 recorded cases. Osteosarcoma and chondrosarcoma have been reported, but also are quite rare—9 proved cases of primary chondrosarcoma of the hand have been recorded according to Lansche and Spjut. Benign lesions of the phalanges and metacarpals are much more frequently encountered.

In 1920, Bloodgood classified central lesions of the phalanges either as chondroma, myxoma, or giant cell tumors. In 1930, Platt reported a series of 13 cystic appearing lesions of the phalanges and metacarpals which he had personally explored. The majority of these were in the proximal phalanx, the index and middle finger being the most common location. Classifying the pathologic process in his specimens, he differentiated simply between chondroma, myxochondroma, and osteitis fibrosa cystica. Of the group of cases he reported, 5 were classified as osteitis fibrosis cystica. Mason and Bunnell in discussing tumors of the hand have stated that enchondroma is the only bone tumor found with any frequency in the phalanges although, on occasion, a giant cell tumor may be found in one of the metacarpals. Mason believed that a true bone cyst was quite unusual in the phalanges.

Vermooten, Cole, and Duskes have reported isolated cases of what have been considered to be true giant cell tumors involving the phalanges or metacarpals of the hand. Meyerding, in 1950, reported that of the 130 cases of giant cell tumors seen at the Mayo Clinic, only 1 was found to involve the hand. This tumor was located in the distal phalanx of the long finger. Murphy and Ackerman have also observed a giant cell tumor of the metacarpal of the thumb, and have included this in their review of 31 cases of giant cell tumor. Posch has recently mentioned that xanthoma of the tendon sheath may very occasionally invade bone. Fletcher, in a review of 43 xanthomas of the tendon sheath found 1 case in which there was involvement of the bone of the thumb.

The benign osteoblastoma or giant osteoid osteoma may be found in the hand. The occurrence of this lesion in the metacarpals has been mentioned in articles by Jaffe and Mayer, Dahlin and Johnson, Jaffe, and Lichtenstein. No mention of aneurysmal bone cyst occurring in the long bones of the hand has been encountered in the literature, and none was found in the review of our pathologic material.

From the Orthopedic Division of the Department of Surgery, Washington University School of Medicine, St. Louis, Missouri.

The enchondroma is a well known entity and its loculated appearance in the roentgenogram is considered to be characteristic, particularly if it is associated with small flecks of calcified cartilage in its center. Other lesions, however, may have a somewhat similar appearance, and it is these that we are primarily interested in presenting this report. During the same period in which 14 enchondromas of the hand were found in our surgical pathology files, 8 other lesions were encountered which demonstrated destruction of the long bones of the hand. (Gout and rheumatoid arthritis were excluded.) This group consisted of 2 cases of giant cell tumor, 2 cases of destructive lesions of the phalanges, which we have had difficulty in classifying (Cases 3 and 4), and 2 cases of cystic lesions of the long bones of the hand, which have proved to be due to hyperparathyroidism. There was 1 case each of a lipoma of the distal phalanx of the thumb and of an inclusion cyst which destroyed bone in the distal phalanx of the thumb. The pertinent findings in these 8 cases are summarized in the following case reports.

CASE 1. H. R., a 29 year old white female, was seen for the first time in 1952 because of pain in the left ring finger. Examination revealed tenderness over the proximal portion of the middle phalanx. Roentgenographic examination revealed a destructive lesion of the proximal portion of the middle phalanx (Fig. 1a). The lesion had a loculated appearance and was initially thought to represent an enchondroma of the phalanx. The lesion was curetted and packed with bone chips. The pathologic diagnosis of benign giant cell tumor was made (Fig. 1b).

Following operation the patient had no symptoms until March 1957. At that time she noted the gradual onset of aching pain in the same finger. Examination on April 3, 1957 revealed fusiform swelling of the middle phalanx of the left ring finger with associated tenderness. The previous operative wound was well healed, and function of the middle finger joint was essentially normal. Roentgenographic examination, at the time of admission, showed a loculated appearing lesion of the middle phalanx of the ring finger, with a similar lesion in the distal portion of the proximal phalanx of the same finger (Fig. 1c). Roentgenographic examination of the opposite hand and skull were procured in order to rule out other similar lesions; none was found. The serum calcium was 10.2 milligrams per cent, the serum phosphorus 3.8 milligrams per cent, and the alkaline phosphatase 2.1 Bodansky units. Routine blood and urine studies were within normal limits.

Because of the recurrence of the tumor and the involvement of the adjacent phalanges, it was decided advisable to amputate the entire fourth finger. This was carried out on April 6, 1957. At the same time a transposition of the fifth finger was done to take the place of the missing fourth finger (Fig. 1d). The patient had an uneventful convalescence. The pathologic specimens from the 1952 and 1957 operations are almost identical in appearance. The tissue is composed of a rather cellular stroma which is made up of a spindle type of cell. In the initial specimen many giant cells were present with centrally located nuclei numbering from 8 to 20 per cell. The cellular stroma of the initial specimen upon review was again considered to be perfectly benign since the cells were regular and mitotic figures were rare. In the specimen of 1957, the tumor had not changed its character significantly, except for the fact that there was more evidence of osteoid formation in the amputated specimen (Fig. 1e).

CASE 2. L. C., a 42 year old white female, had a history of aching and swelling of the first metacarpal of the left hand for approximately 1½ years. Examination revealed fusiform swelling in the region of the first metacarpal of the left hand which was tender to palpation. The patient was admitted to the hospital on January 14, 1946. Roentgenographic examination revealed a lesion which had practically destroyed the entire base of the first metacarpal (Fig. 2a). Alkaline phosphatase was 1 Bodansky unit. The blood calcium was 11.8 milligrams per cent, the blood phosphorus level was 4.3 milligrams per cent. The remainder of the physical examination was essentially negative. Biopsy of the lesion revealed a giant cell tumor of the metacarpal (Fig. 2b). The tumor was considered to be benign, and the patient received a course of roentgen therapy as definitive treatment.

In September 1946, the patient returned because she was still having pain in the thumb. At that time, a resection of the metacarpal was carried out, and the defect was filled with a tibial bone graft. Following this operative procedure, the patient had a satisfactory course until October 1956, at which time she was readmitted because of an infection at the operative site. Sequestrectomy of the graft was carried out, and the postoperative course following this was essentially benign.

The biopsy of January 16, 1946 revealed sheets of spindle shaped cells, with rather large and vesicular nuclei. The cells did not vary significantly in size and mitotic figures were rare. The stroma was considered to be benign. Intermixed in this fibrous tissue-like stroma were many large giant cells which contained 10 to 30 centrally placed nuclei. Occasional areas of osteoid formation were seen in the biopsy specimen (Fig. 2b).

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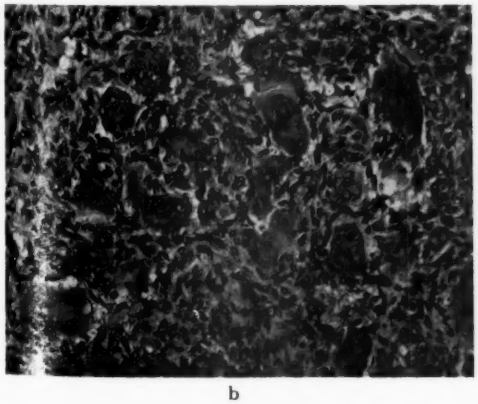
d



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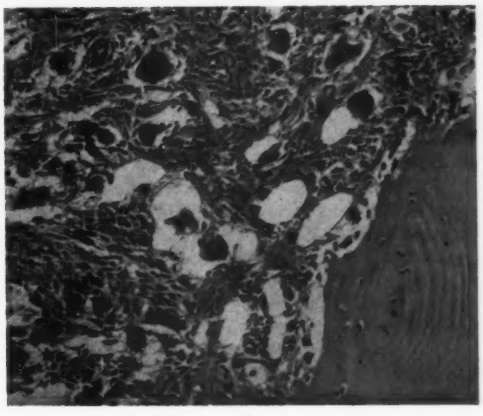

e

FIG. 1. Case 1. a, Initial roentgenogram of giant cell tumor of the middle phalanx of the ring finger. Note the cystic appearance of the lesion with slight expansion of the cortex. b, Photomicrograph (×161) of initial tumor. Microscopically this was considered to be a typical giant cell tumor of bone. c, X-ray appearance of the recurrent giant cell tumor 5 years after the initial removal. Note the involvement of the proximal phalanx. d, Amputation of the fourth finger with transposition of the fifth finger was the method of management in this recurrent giant cell tumor. e, Photomicrograph (×161) of the recurrent giant cell tumor. In the recurrent tumor osteoid formation was more evident.

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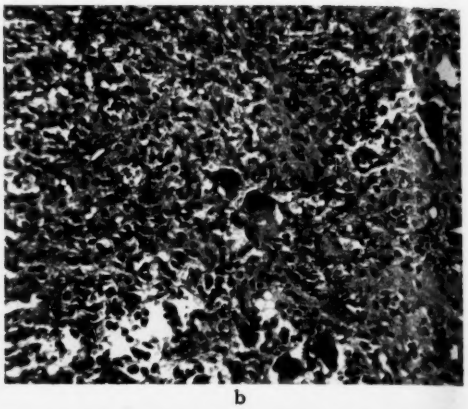

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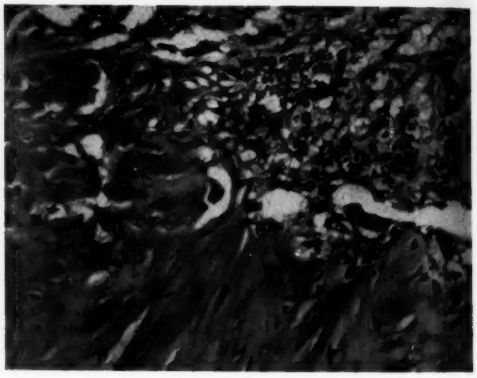

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FIG. 2. Case 2. a, Initial roentgenogram[1] of a giant cell tumor of the first metacarpal. b, Photomicrograph (×117) of tumor. This lesion is a benign giant cell tumor. c, Photomicrograph (×147) of persistent giant cell tumor. The adjacent hyalinized material with scanty nuclei is considered to be radiation effect upon the tumor.

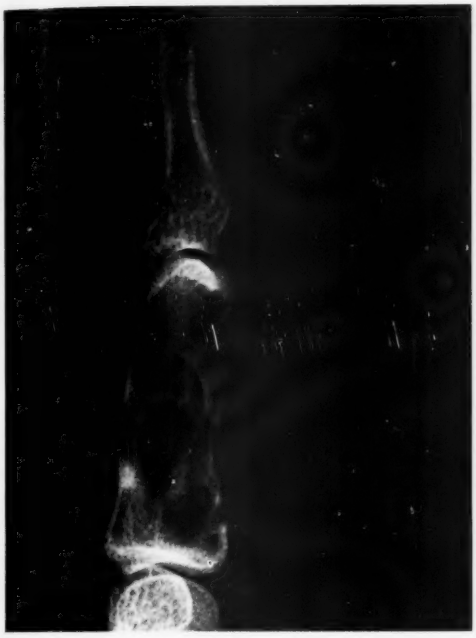
In spite of radiation therapy, the amputation specimen revealed persistent tumor which did not vary significantly from the original specimen. There were, however, large areas of homogeneous eosinophilic staining material which were considered to represent the radiation effect upon the tumor (Fig. 2c). In these areas there was a striking absence of nuclei.

CASE 3. M. C., a 35 year old female, was seen on July 20, 1956 because of pain in the little finger of the right hand. Examination revealed mild fusiform enlargement of the middle phalanx of the finger. Function of the finger was essentially normal. Roentgenograms showed enlargement of the middle phalanx, with multiple areas of radiolucency involving the entire middle phalanx (Fig. 3a). There was some expansion of the cortex. The initial diagnosis was enchondroma. The patient was admitted to the hospital on July 22, 1956, and the lesion was excised as completely as possible. The bony defect was filled with autogenous iliac bone, and the postoperative course was uneventful.

The nature of the material removed raised the question of a diagnosis of hyperparathyroidism. Accordingly, blood chemistries were obtained while the patient was still in the hospital. The calcium was 10 milligrams per cent; the phosphorus 3.3 milligrams per cent; the alkaline phosphatase 2.2 Bodansky units. The urinalysis was negative, and a urine Sulkowitch test was also considered to be within normal limits.

The tissue submitted was composed for the most part of a fibrous tissue stroma (Fig. 3b). This stroma was well oriented, the cells were of uniform size, and mitotic figures were very rare. Interspersed in this fibrous tissue stroma were numerous giant cells. These cells had dark staining nuclei numbering from 4 to 16, which were centrally located within the cells (Fig. 3c). Also interspersed in this fibrous tissue stroma were well defined areas of osteoid formation (Fig. 4b). The degree of osteoid formation appeared to be in excess of that usually seen in giant cell tumors

[1]Editors' note: An exception has been made in the policy of the Editors in republishing this roentgenogram, which appeared in *Cancer*, 1956, 9: 317, Fig. 1 (14), in order to fully document this case with the correlative pathologic photomicrographs.



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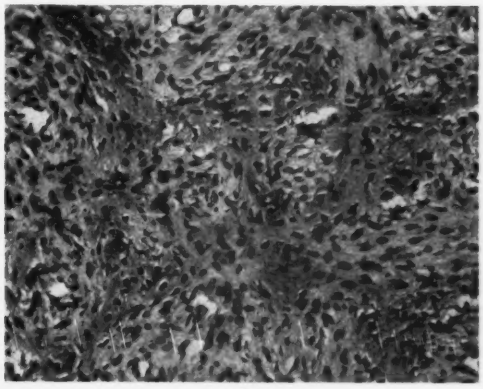

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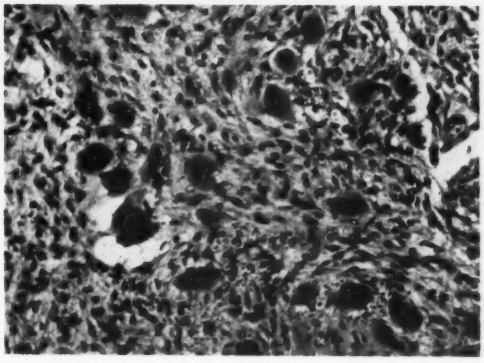


c

FIG. 3. Case 3. a, Initial roentgenogram of lesion. Note the loculated appearing destructive lesion of middle phalanx of little finger. b, Photomicrograph (×109) of area showing predominantly a fibrous tissue stroma. There is some osteoid formation. c, Photomicrograph (×106) of same lesion. In this area giant cells predominate in a fibrous tissue stroma (see Fig. 4b).

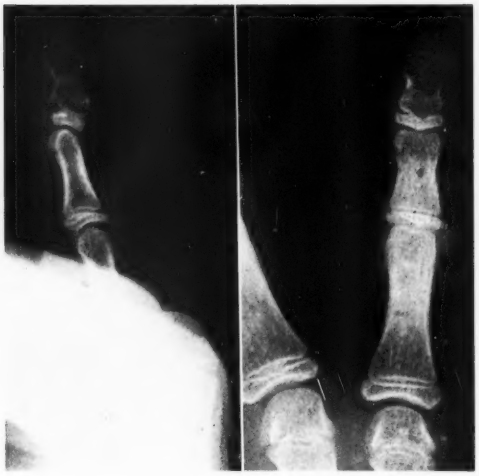
of bone. Some of this osteoid showed evidence of calcification. The stroma, though quite cellular, was arranged in strands and swirls and was considered to be benign.

Subsequent roentgenograms have revealed satisfactory consolidation of the bone graft, but there has persisted to date an area of radiolucency in the extreme distal tip of the middle phalanx which is thought to represent residual tumor. Over the course of a year, however, this has shown no significant change. The patient has regained a normal range of motion of the fifth finger, according to her surgeon's report, and there have been no complaints referable to the finger.

CASE 4. W. G., a 10 year old white girl, was considered to be in excellent health until December 1956. At that time it was noted by the parents that the tip of the little finger of the right hand was enlarged. Roentgenographic examination of the patient's hand revealed evidence of tumor formation involving the bone and soft tissue of the distal phalanx of the little finger (Fig. 4a). There was extensive destruction of the distal phalanx. The epiphysis appeared to be relatively normal, but the entire diaphysial and metaphysial portion of this phalanx was expanded. The roentgenologist reported that this probably represented a chondroma or enchondroma of the phalanx. The remainder of the examination of this patient was essentially negative. Roentgenograms of the chest showed that there was no evidence of metastatic lesions.

Amputation of the distal phalanx of this finger was carried out because of the extensive nature of the lesion. Upon sectioning the tissue, the tumor mass was described as having a grayish-yellow appearance and was easily shelled out of the finger tip. The patient made an uneventful recovery, and to date there has been no evidence of recurrence of the lesion.

The microscopic appearance of the lesion revealed a fibrous tissue stroma which was moderately cellular. Mitotic figures in the stroma were very rare. It was arranged in strands and the cells appeared to be fairly uniform in size. The stroma was considered to be benign. The fibrous tissue stroma arrangement was interrupted by a considerable amount of osteoid



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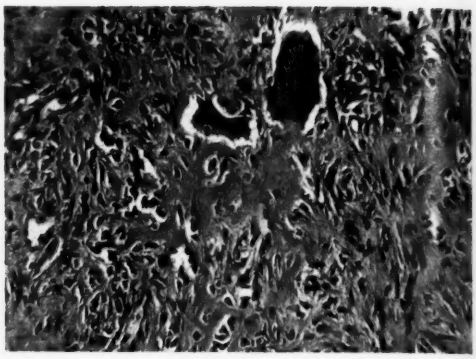

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FIG. 4. Case 4. a, Initial roentgenogram. This lesion was composed of a fibrous tissue stroma, abundant osteoid formation. Note the extensive destruction of the distal phalanx with complete preservation of the epiphysis. b, Photomicrograph (×106) of the lesion. This lesion was similar to that in Case 3. In this particular area the three components of the lesion can be seen: a fibrous tissue stroma, giant cells, and abundant osteoid formation.

formation and interspersed giant cells (Fig. 4b). The giant cells had the usual pink staining cytoplasm with from 4 to 30 centrally located nuclei. Toward the edge of the lesion there was marked destruction and erosion of cortical bone, with extension of the tumor into the soft tissues. In many areas it was almost impossible to differentiate this tumor from a giant cell tumor. However, with the areas of marked osteoid formation, some of which was calcifying, it was thought that this did not represent a giant cell tumor and in all respects was similar to the lesion found in Case 3.

CASE 5. M. A., a 70 year old colored female, had noted a small lump on the flexor surface of the right thumb for 3 years. During the 3 to 4 months prior to seeking advice, the mass had increased in size and had become painful and tender to touch.

Examination revealed a lobulated mass of firm consistency over the ulnar side of the distal phalanx of the thumb. The mass did not move with flexion of the thumb and appeared to fill most of the pulp of the thumb. The mass was neither hot nor fluctuant. There was mild tenderness when the mass was compressed. Roentgenographic examination revealed a destructive lesion in the proximal portion of the distal phalanx (Fig. 5a). A diagnosis of giant cell tumor, probably of tendon sheath origin, was made in this instance.

On March 21, 1955, under general anesthesia, the tumor was removed. A firm lobulated mass was encountered and easily dissected from fatty tissue of the thumb. Three distinct lobules of tumor were removed from the pulp of the thumb, and the tumor was then traced to the base of the volar aspect of the distal phalanx. A small opening into the distal phalanx was encountered, and when this was opened 2 to 3 loculated areas of tumor were traced down into the phalanx. The appearance of the inside of the phalanx was somewhat like honeycomb stone. The small cystic compartments had smooth firm bone as their walls.

The specimen was a lobulated tumor, yellow in color, and slightly firm. There was a definite fibrous tissue-like capsule about the tumor. The substance of the tumor consisted entirely of fat cells, with no evidence of malignancy and no evidence of giant cells. It was thought that this represented a lipoma. Whether this lipoma arose from the pulp of the thumb and invaded the bone or whether it arose from the bone and invaded soft tissue we believe is impossible to answer (Fig. 5b).

CASE 6. M. B., a 69 year old white woman, presented herself with a nonpainful swelling of the left thumb in January 1958. The mass had been present for 9 to 10 months. About a year prior to the initial visit the patient had been stuck in the same thumb by a rose thorn.

Examination revealed a firm but fluctuant mass over the ulnar aspect of the distal phalanx of the thumb. It was neither tender nor hot. Roentgenographic examination revealed marked destruction of approximately 50 per cent of the volar aspect of the distal phalanx of the left thumb (Fig. 6).

On January 13, 1958 exploration was carried out under local anesthesia with a tourniquet in place. The mass was found to be filled with a cheese-like material which could be easily curetted from the cystic cavity. After removal of the contents, the entire lining of the cystic lesion was easily removed from the eroded distal phalanx. Grossly this lesion

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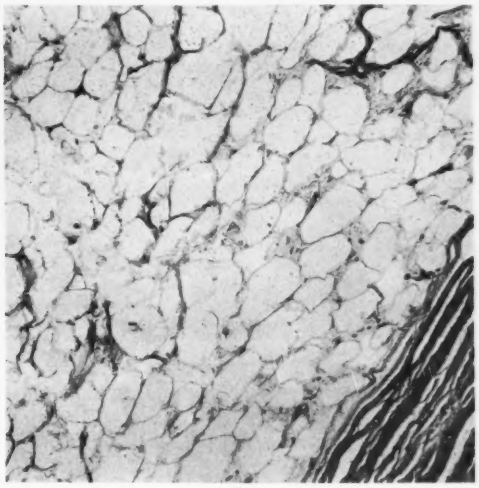

b

FIG. 5. Case 5. a, Initial roentgenogram of a destructive lesion of the distal phalanx of the thumb. Histologically this lesion was a lipoma. b, Photomicrograph (×50) of a lipoma which partially destroyed the distal phalanx of the thumb.

appeared to be an epidermal inclusion cyst, and this was confirmed upon microscopic examination of the cyst wall.

CASE 7. E. D., a 56 year old white female, was admitted to the hospital in March 1927 with a 2 year history of swelling and pain in the proximal phalanx of the right index finger.

Examination revealed atrophy and marked motor weakness of both lower extremities. The knee jerks were equal and active bilaterally; but the ankle jerks were absent bilaterally. There was marked gluteal muscle weakness. Examination of the hand revealed that the proximal phalanx of the right index finger was swollen. It was neither tender, nor red. The white blood cell count was 4,100. The red blood cell count was 4.5 million; the nonprotein nitrogen was 26.2; the Wassermann reaction was negative. Roentgenographic examination of the abdomen revealed bilateral nephrolithiasis. Roentgenographic examination of the finger revealed that there was a cystic appearing lesion with erosion of the cortex, and expansion of the entire phalanx. A biopsy of the proximal phalanx of the right index finger was done, and according to the surgeon's report a red, rubbery, incapsulated tumor was identified and removed by curettement. Considerable discussion of the pathologic tissue ensued, and it was eventually thought that this represented a malignant bone sarcoma and consequently, amputation of the finger was done.

Review of the pathologic specimen now reveals that this tumor was composed of very cellular stroma. The cells were of the spindle cell variety and were arranged in swirls and strands. These cells had oval nuclei and mitotic figures were quite rare. Interspersed in this fibrous tissue stroma were numerous giant cells containing from 10 to 50 centrally arranged nuclei. Very little osteoid formation is apparent in the biopsy slide; however, there is definite evidence of osteoid formation (Fig. 7).

Following amputation of the finger, the patient returned home and did not re-enter the hospital until September 1928. The second admission was occasioned by the appearance of a tumor in the maxillary region. The tumor mass in the jaw was found by the patient's dentist when he removed a painful tooth. Examination was essentially the same, except that now there was a cystic lesion of the right ulna. A biopsy of this lesion was carried out in September 1928, and the pathologic interpretation was that it was a tumor similar to the one found in the finger.

Following removal of the lesion from the ulna, however, further investigation was carried out. The calcium was found to be 15.9 milligrams per cent; the phosphorus 1.4 milligrams per cent; and the nonprotein nitrogen 13. It then became apparent that the patient was suffering not from a malignant tumor of the phalanx or the ulna, but that the actual pathologic process was that of hyperparathyroidism. Accordingly, on August 2, 1928 exploration of the neck was carried out and a parathyroid adenoma on the left side was found and removed. In the postoperative period the patient had a stormy course.

FIG. 6.

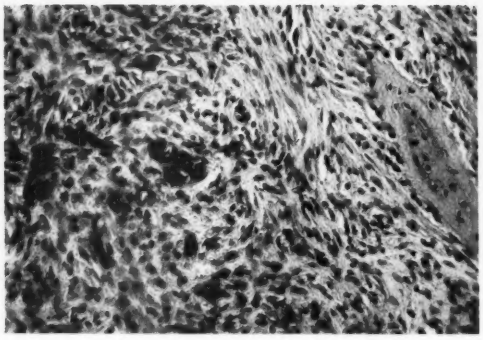

FIG. 7.

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FIG. 8.

FIG. 6. Case 6. Roentgenogram of a destructive lesion of the distal phalanx of the thumb. Pathologically this was a typical inclusion cyst which had eroded into the bone.

FIG. 7. Case 7. Photomicrograph (×151) of the lesion of the proximal phalanx of the right index finger in a patient with a proved parathyroid adenoma. The lesion has a cellular stroma arranged in swirls and strands. Giant cells were present. Osteoid formation is apparent about a spicule of bone.

FIG. 8. Case 8. a, Roentgenogram of the hands of a patient with a proved parathyroid adenoma. Note the destructive lesion in the fifth metacarpals. b, Roentgenogram 9 months after removal of the parathyroid adenoma. The tumor was encapsulated, benign, and composed mostly of chief cells. Note the dense reossification of the previously existing cystic lesions of the fifth metacarpals.

She had repeated bouts of severe tetany which required vigorous treatment. These episodes persisted for several months while the patient was in the hospital. On numerous reports a calcium as low as 4.5 milligrams per cent was recorded. The patient eventually made a good recovery from her episodes of tetany but died some 14 months after operation from urinary tract infection.

CASE 8. C. P., a 38 year old white female, gave a history of having had aching pain in her feet, the anterior portion of the legs, and the right hip for 3 years. About 2 months prior to entering the hospital she had a fall, following which, swelling developed over the right fifth metacarpal. About 1 month prior to admission she consulted her physician because of fatigue and the previously mentioned symptoms. Roentgenograms of the hands, legs, and skull revealed cystic appearing lesions in both fifth metacarpal heads (Fig. 8a). Associated with the cystic lesions was a ragged appearance of the margins of the phalanges suggesting subperiosteal rarefaction.

Blood studies revealed a serum calcium of 11.4 milligrams per cent; a serum phosphorus of 2.0 milligrams per cent; and an alkaline phosphatase of 19 Bodansky units. On February 12, 1957, a typical parathyroid adenoma was removed, occupying the position of the right inferior parathyroid gland. The adenoma was encapsulated and composed for the most part of chief cells. It was considered to be a benign lesion. Postoperatively the patient did very well, and in 9 months showed reossification of the cystic lesions in the metacarpals (Fig. 8b).

DISCUSSION

The review of our material again confirms the fact that enchondroma is the most common lesion to destroy bone in the phalanges of the hand. One-third of the destructive lesions of the long bones of the hand in this group of cases, however, were not due to enchondroma.

The giant cell tumors, the hyperparathyroidism and the inclusion cyst need no comment since they are well recognized conditions. To our knowledge the lipoma of the distal phalanx of the thumb is the only recorded case of a lipoma destroying bone in one of the phalanges of the hand. We cannot be sure whether the lipoma arose from the medullary canal of the bone or had an extra osseous origin with secondary invasion. The deep and loculated penetration of the lesion in the phalanx only suggests intraosseous origin.

The pathologic material from Cases 3 and 4 is of particular interest. The histologic pattern does not fit any of the known lesions that occur in the hand. The prominent vascular spaces and the characteristic osteoid of the benign osteoblastoma are absent. The amount of osteoid formation is distinctly less than in osteoblastoma but certainly more than one would expect to observe in a giant cell tumor. We do not believe these two lesions are giant cell tumors. The lesions were localized to a single bone of the hand, and the patients had no evidence of a generalized disease such as hyperparathyroidism.

This lesion is characterized clinically by mild pain, swelling, and a roentgenographic picture of both central and cortical bone destruction. Histologically the lesion is characterized by a benign fibrous tissue stroma. Moderately abundant osteoid, some of which shows early calcification, is readily seen in the microscopic sections. In some areas large numbers of multinucleated giant cells are found while in other areas they are much less conspicuous.

There is no evidence that these cases represent an inflammatory or traumatic lesion. It is more likely that this is a benign neoplastic process. We do not have a particularly good name for this lesion but believe it to be a distinct entity and should therefore be designated. The term osteoid fibroma most clearly denotes the histologic components and is therefore suggested as an appropriate name.

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A CLINICOPATHOLOGIC STUDY OF 172 PATIENTS WITH PRIMARY CARCINOMA OF THE OVARY

JOHN C. TURNER, JR., M.D., WILLIAM H. REMINE, M.D., F.A.C.S., and MALCOLM B. DOCKERTY M.D., Rochester, Minnesota

PROGRESS in improving the survival rates from carcinoma of the ovary in the past several decades has been relatively slight. The insidious onset of the disease frequently results because the early stage has not been recognized by either patient or physician. Because of the unfavorable prognosis reported in past years, we believed it best to evaluate the current results from the surgical treatment of primary carcinoma of the ovary.

MATERIALS AND METHODS

The present series is comprised of cases of primary carcinoma of the ovary encountered at the Mayo Clinic during the years 1945 through 1949. In all cases the treatment was surgical, and the diagnosis of carcinoma was proved by multiple histologic sections. In every case the clinical data as well as the pathologic material were reviewed. Cases of metastatic (secondary) carcinoma of the ovary were excluded as were those of functioning ovarian tumors such as granulosa cell tumors, arrhenoblastomas, and dysgerminomas. Furthermore, cases in which the primary operation was not performed at the clinic, that is, cases in which recurrent carcinoma of the ovary was found elsewhere, were likewise excluded. During the 5 year period covered by this study 172 cases met the afore-mentioned requirements, and these comprise the basis of this study.

RESULTS

The youngest patient was 23 and the oldest was 79 years of age. The mean age was found to be 52.7 years with the peak age incidence in the sixth decade (50 to 59 years).

Of the 172 patients, 147 were married and 25 were single, which gave a ratio of about 6: 1.

Seventy-one patients were nulliparous and 95 were multiparous. Data concerning parity were not recorded in 6 cases.

The family history was negative for carcinoma in 115 and positive in 53 cases. Information relative to this subject was not available in 4 cases.

Symptoms. Abdominal pain and swelling were the commonest symptoms; they were noted in 47.7 and 43.6 per cent of the cases respectively (Table I). Symptoms referable to the urinary tract were the next commonest presenting complaint. Mostly these were urgency and frequency due to pressure from the adjacent tumor. Carcinoma was an "unsuspected finding" in 10.5 per cent of cases, and the tumor was discovered in 9.9 per cent of patients because of some abnormal vaginal bleeding. A "heavy (dragging) sensation" in the pelvis was noted by 9.3 per cent of the patients.

The average duration of symptoms was 5.9 months, the range being from 1 week to 4 years. Eighteen patients were asymptomatic and the duration of symptoms was not recorded in 9 cases.

Clinical stages of ovarian cancer. In order to evaluate the results of surgical therapy, it seemed well to establish clinical stages of development of the disease. A review of the literature did not show unanimity of opinion regarding stages of the disease. We are of the opinion that any such classification should take into consideration the findings

From the Sections of Surgery and Surgical Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

TABLE I.—SYMPTOMS IN 172 PATIENTS WITH PRIMARY CARCINOMA OF THE OVARY

Symptoms	*No. of cases*	*Per cent*
Abdominal pain	82	47.7
Swelling	75	43.6
Urinary tract symptoms	24	14.0
Unsuspected finding	18	10.5
Vaginal bleeding	17	9.9
"Heavy sensation in pelvis"	16	9.3
Intestinal obstruction	7	4.1
Loss of weight	6	3.5
"Febrile type reaction"	4	2.3
Heart failure	3	1.7
Meigs' syndrome	1	0.6

at the time of surgical exploration. The stages of ovarian cancer as described by Davis and associates, and by Munnell and Taylor, seemed valid and our classification is similar to classifications they have presented.

On the basis of the findings at the time of surgical exploration the following classification of clinical stages was adopted: Stage 1, carcinoma confined to the ovary. The growth may be solid or cystic, but it does not contain excrescences of infiltrated adhesions. Stage 2, breakthrough of the ovarian capsule, present in the form of excrescences, infiltrated adhesions, or ruptured capsule (before or at operation). This stage also includes bilateral ovarian involvement without evidence of any other pelvic metastasis. Stage 3, pelvic dissemination with involvement of tubes, uterus, other ovary, bladder, rectum, rectosigmoid, or pelvic peritoneum. Stage 4, metastasis beyond the pelvis to the liver, omentum, and upper portion of the abdomen. The distribution of our cases according to this classification was as follows: stage 1, 39 cases (22.7 per cent); stage 2, 37 cases (21.5 per cent); stage 3, 52 cases (30.2 per cent); stage 4, 44 (25.6 per cent).

A comparison of clinical stage with duration of symptoms showed that there was no true correlation.

SURGICAL PROCEDURES

Previous abdominopelvic operation. Previous abdominopelvic operation had been performed on 26 patients (15.1 per cent) (Table II). Sixteen patients were less than 40 years of age at the time of the initial operation; 5 patients were in the age group 40 to 44 years, and 5 patients were 45 years of age or older. Hysterectomy had been performed prior to the operation for carcinoma of the ovary in 14 cases (8.1 per cent of the total group of cases). In about 88 per cent of these patients the interval between the previous pelvic operation and discovery of the carcinoma was 5 years or more; the average interval was 10 years.

TABLE II.—PREVIOUS ABDOMINOPELVIC OPERATION IN PATIENTS WITH PRIMARY CARCINOMA OF THE OVARY

	Age (yrs.)	
Operation	*At first operation*	*At operation for cancer*
Vaginal hysterectomy (for prolapse)	61	69
Left salpingectomy (for tubal pregnancy)	22	47
Myomectomy	43	56
Subtotal hysterectomy, right salpingo-oophorectomy	37	57
Vaginal hysterectomy and anteroposterior repair (menorrhagia, pelvic relaxation)	42	47
Excision, bleeding corpus luteum cyst of right ovary	35	56
Removal, benign ovarian cyst, right	26	75
Total abdominal hysterectomy	37	67
Right salpingo-oophorectomy (benign cyst)	48	63
Uterine suspension	30	50
Total abdominal hysterectomy, left salpingo-oophorectomy (fibroids), right ovary "normal"	48	55
Subtotal abdominal hysterectomy	43	61
Vaginal hysterectomy and repair	58	67
Subtotal hysterectomy	33	48
Total abdominal hysterectomy, right salpingo-oophorectomy	46	54
Total abdominal hysterectomy, left salpingo-oophorectomy	39	54
Subtotal abdominal hysterectomy	44	49
Salpingo-oophorectomy, right	28	30
Oophorectomy, left	30	45
Salpingo-oophorectomy, left	32	56
Salpingo-oophorectomy, right (ectopic pregnancy)	24	32
Total abdominal hysterectomy	34	52
Uterine suspension; excision, cyst (benign), right ovary	22	25
Salpingo-oophorectomy, right	28	58
Oophorectomy, left; total abdominal hysterectomy	36	39
Cervical amputation (metaplasia); vaginal hysterectomy and repair (same patient)	41	45
	42	45

Surgical procedures utilized. Various surgical procedures were utilized (Table III). Combined total abdominal hysterectomy and bilateral salpingo-oophorectomy was the procedure performed most frequently. Bilateral salpingo-oophorectomy was usually performed as a palliative procedure and

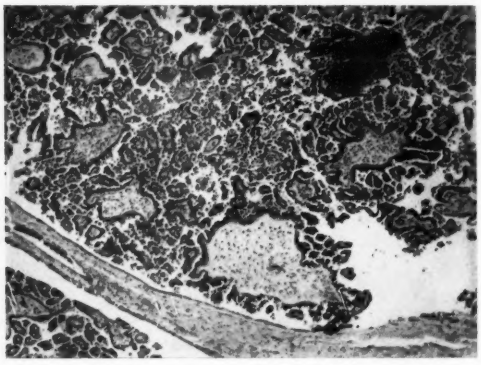

FIG. 1. Papillary serous cystadenocarcinoma, grade 2. Hematoxylin and eosin, ×42.

unilateral salpingo-oophorectomy was done as a conservative measure in a few young women who desired a family and had localized disease. The patients in whom vaginal hysterectomy was performed were those in whom ovarian carcinoma was detected as an "incidental finding" at the time of operation for descensus uteri.

Operative mortality. Five of 172 patients died in the immediate postoperative period giving a hospital mortality rate of 2.9 per cent. Two patients died as the result of cardiac arrest at the time of operation, 2 patients died as a result of postoperative shock, and 1 patient died of pulmonary embolus the day after operation.

Effect of rupture or "spillage." Rupture of the cystic component of the ovarian tumor occurred before operation in 3 cases, and 19 patients sustained "accidental" rupture of the tumors during the process of removal. Of the 3 patients with this complication, 1 died of recurrent carcinoma, 1 is living with abdominal metastasis, and 1 patient has lived more than 5 years with no sign of recurrence. Of this group in which the cystic component of the tumor was ruptured preoperatively, 2 patients had localized disease and cure seemed possible at the time of initial operation.

Nine, or 47 per cent, of the 19 patients in whom the tumor was ruptured during surgical removal are living 5 to 11 years later. Eight of these 9 patients had localized disease (stage 1). One patient with a stage 3 lesion received additional postoperative x-ray therapy. Ten of the 19 patients whose tumors were accidentally ruptured during removal are dead: 1 died as a result of the operation, 3 died of unrelated causes, and 6 died of recurrent disease or persistent carcinoma. Two of these 6 survived 8 years after operation before death due to carcinoma. Only 2 patients of those dying with recurrent cancer had localized disease (stage 1 or 2); the rest had extensive malignant involvement (stage 3 or 4) at exploration.

TABLE III.—SURGICAL PROCEDURES UTILIZED FOR PRIMARY CARCINOMA OF THE OVARY

Procedure	*No. of cases*	*Per cent*
Total abdominal hysterectomy, bilateral salpingo-oophorectomy	69	40.1
Bilateral salpingo-oophorectomy	34	20.0
Abdominal exploration, removal of specimen for biopsy	20	11.6
Unilateral salpingo-oophorectomy	13	7.6
Subtotal abdominal hysterectomy, bilateral salpingo-oophorectomy	12	7.0
Unilateral oophorectomy	8	4.7
Vaginal hysterectomy, bilateral salpingo-oophorectomy	2	1.2
Total abdominal hysterectomy, bilateral salpingo-oophorectomy with resection of portion of intestine	3	1.7
Total abdominal hysterectomy, unilateral salpingo-oophorectomy	3	1.7
Unilateral salpingo-oophorectomy, partial oophorectomy	1	0.6
Wertheim hysterectomy	1	0.6
Unilateral oophorectomy, bilateral salpingectomy	2	1.2
Subtotal abdominal hysterectomy, right salpingo-oophorectomy	1	0.6
Left salpingectomy, excision of portion of bowel	1	0.6
Subtotal abdominal hysterectomy, unilateral salpingo-oophorectomy	2	1.2

OTHER TREATMENT

Roentgen therapy. During the period January 1945 through December 1949, 95 of 172

TABLE IV.—CLINICAL STAGES OF PRIMARY CARCINOMA OF THE OVARY AS CORRELATED WITH TREATMENT

		Treatment			
		Surgical		*Surgical with radiation*	
Stage of involvement	*Total No. of cases*	*Cases*	*Per cent*	*Cases*	*Per cent*
1	39	25	64.1	14	35.9
2	37	24	64.9	13	35.1
3	52	16	30.8	36	69.2
4	44	12	27.3	32	72.7

patients (55.2 per cent) with primary carcinoma of the ovary received postoperative radiation therapy. For the most part, this treatment was given later for palliation. A small number of patients received more than one course of radiation therapy ranging from 1,000 to 5,000 roentgens. Results of such treatment were difficult to evaluate.

Clinical stages and treatment. An analysis of the treatment received as correlated with the clinical stage of the disease is presented in Table IV. It may be noted that patients having stages 1 and 2 of the disease were treated mainly by surgical procedures, some being given prophylactic radiation therapy when circumstances warranted. As might have been predicted, patients having more advanced stages of the disease received both surgical and radiation therapy.

PATHOLOGIC FEATURES

The microscopic material was reviewed in every case and, when necessary, additional sections were cut from the preserved gross specimens in order to secure adequate material for classification. The tumors were grouped histologically as to type by one of us (M.B.D.) by means of a modification of the classification presented by Glynn, and they were divided further according to the degree of anaplasia, employing Broders' method of grading (Table V). The commonest type of tumor was the papillary serous cystadenocarcinoma, which was found in slightly less than half (44.8 per cent) of the cases. This group of tumors, together with the mucous and the mixed mucous and serous cystadenocarcinomas, tended to be of a low grade of malignancy (Broders', grade 1 and 2). As might be anticipated, the seroanaplastic and so-called endometrial types of adenocarcinoma, together with the hypernephroid type and teratomas, were high grade lesions (Broders', grades 3 and 4).

Papillary serous cystadenocarcinomas. These lesions were present in 77 cases, or 44.8 per cent of the total number. Synonyms used in describing them included papillary adeno-

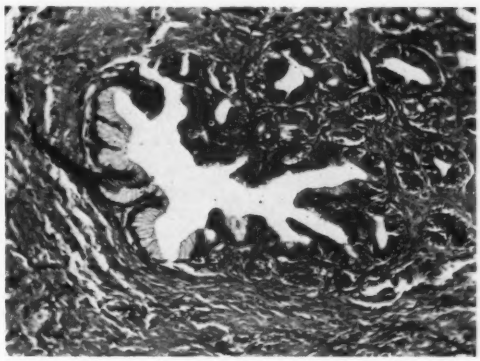

FIG. 2. Mucous type of cystadenocarcinoma, grade 2. Hematoxylin and eosin, ×88.

carcinoma and endosalpingoma, a form of adenocarcinoma. On gross examination the usual picture was that of a cyst, either unilocular or multilocular, containing intracystic and extracystic papillary excrescences. The walls of the cysts were smooth in some cases and rough in others. In some cysts, solid masses projected cauliflowerlike within the interior. Microscopically (Fig. 1), the

TABLE V.—PRIMARY CARCINOMA OF THE OVARY: PATHOLOGIC CLASSIFICATION, INCIDENCE OF TYPES, GRADE OF MALIGNANCY

Pathologic type	*No. of cases*	*Per cent of total*	*Grade of carcinoma (Broders' method)* 1	2	3	4
Papillary serous cystadenocarcinoma	77	44.8	43	18	15	1
Mucous type cystadenocarcinoma	21	12.2	15	4	1	1
Mixed serous and mucinous type cystadenocarcinoma	4	2.3	3	1	0	0
Seroanaplastic type adenocarcinoma	37	21.5	0	0	20	17
Endometrial type adenocarcinoma	19	11.0	5	11	3	0
Adeno-acanthoma endometrial type (6)			1	4	1	0
Adenocarcinoma-endometrial type (13)			4	7	2	0
Mesonephroma type adenocarcinoma	8	4.7	0	0	3	5
Teratoma associated with carcinoma	3	1.7	0	0	0	3
With adenocarcinoma and fibrosarcoma (1)			0	0	0	1
With squamous cell epithelioma arising in a teratoma (1)			0	0	0	1
With malignant struma ovarii (1)			0	0	0	1
Hypernephroid type adenocarcinoma	3	1.7	0	0	1	2

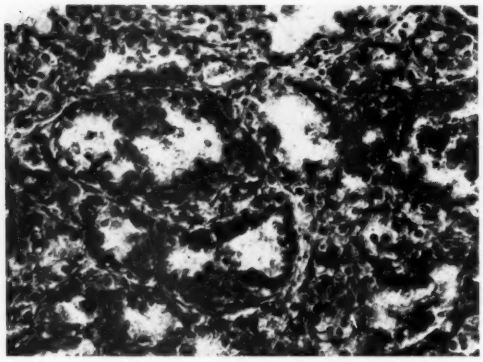

FIG. 3. Seroanaplastic type of adenocarcinoma. Hematoxylin and eosin, ×120.

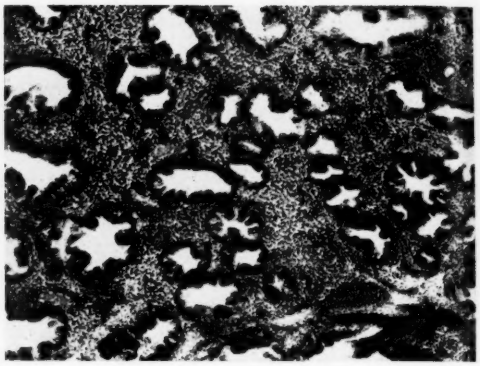

FIG. 4. Endometrial type of adenocarcinoma showing adeno-acanthoma variant. Hematoxylin and eosin, ×54.

picture was one of cores of papillary edematous connective tissue mantled by multiple layers of short or tall columnar cells. Psammoma bodies with concentric regions of hyaline necrosis and calcification were common. Mitosis frequently was present.

Mucous cystadenocarcinoma. These lesions, also known as pseudomucinous cystadenocarcinoma, were present in 21 cases, or 12.2 per cent of the total number. Grossly, these tumors were partially solid and partially cystic. When ruptured they were sometimes associated with myxoma peritonei or "jelly belly." In this latter situation the abdomen was filled with amber gelatinous material.

Microscopically (Fig. 2), a variable pattern was seen. Most of the tumors were of low grade malignancy and exhibited definite gland formation. The gland spaces were lined with columnar cells with basal or central nuclei, and apical mucous droplets were present. At the other extreme were certain anaplastic tumors with poor differentiation into irregular glands, sometimes with scatterings of signet-ring cells.

TABLE VI.—CLINICAL STAGE OF DEVELOPMENT CORRELATED WITH DEGREE OF MALIGNANCY

Stage of development	*No. of cases according to grade of malignancy (Broders')*			
	1	*2*	*3*	*4*
1	26	9	1	3
2	20	10	3	4
3	18	10	19	5
4	5	11	16	12

Mixed mucinous and serous cystadenocarcinomas. In 4 cases the lesions were classified thus, because they demonstrated features of both of the two preceding types.

Seroanaplastic type of adenocarcinoma. This type of highly malignant tumors, present in 37 cases (21.5 per cent), was characterized by atypical epithelial proliferation. Grossly, it was manifested in a variety of forms—cystic, solid, and "mixed." The outer walls were often smooth with bulky and solid rather than fine or papillary intracystic excrescences. In other examples solid extracystic bosselations were present. Barzilai has given the best description of the microscopic picture presented by these neoplasms (Fig. 3). She finds pure and mixed pictures of cells which may be basically small dark cells, large clear cells, or wild syncytial-like anaplastic cells. Arrangement of these cells occurs in all patterns, from the orderly papillary architecture in some of the less malignant examples, through adenopapillary to medullary and diffuse patterns in which cellular differentiation may not be apparent. A serous cystadenocarcinomatous nature is implied by virtue of the "seroanaplastic" designation, but histogenetic signs are overshadowed by manifest anaplasia.

Endometrial type of adenocarcinoma. This tumor presented in both solid and cystic forms with and without extracystic projections in 19 cases (11.0 per cent). The

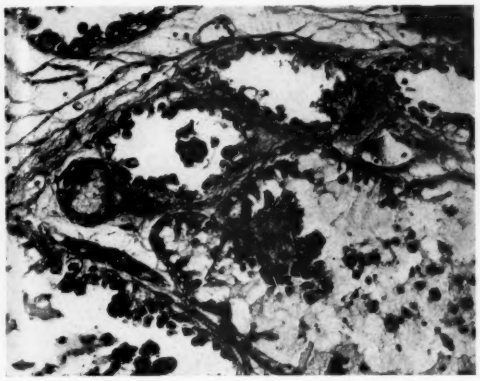

FIG. 5. Mesonephroma type of adenocarcinoma. Hematoxylin and eosin, ×145.

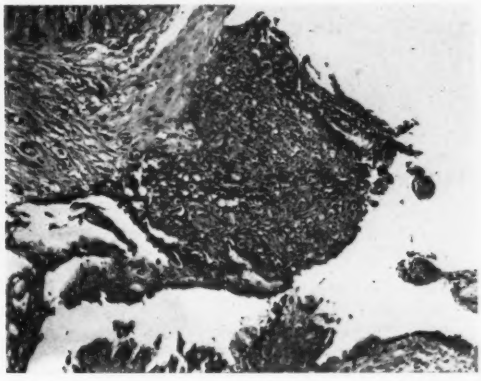

FIG. 6. Carcinoma associated with teratoma. Hematoxylin and eosin, ×73.

growths often were associated with zones of ancient hemorrhage. Microscopically (Fig. 4), an architectural pattern which closely simulates that of endometrial adenocarcinoma was the criterion for inclusion in this group. Tall columnar cells were seen which tended to form glands in tumors of lower grades of malignancy. Basically, a small dark cell and a large clear cell type are noted. A few (6) were adeno-acanthomas. In Glynn's series the tumors often had spread beyond the confines of the ovary.

Mesonephroma. The term "mesonephroma type of adenocarcinoma" was first used by Schiller to describe an epithelial ovarian tumor which he considered to derive from fetal remnants of the mesonephros which develops near the ovary. This type of tumor was present in 8 cases (4.7 per cent). Grossly, tumors falling into this category were partly solid. Microscopically, they displayed small epithelial-lined locules. Epithelial-mantled tufts, the constituent cells of which had "hob-nail" nuclei, projected from the walls of the locules. The tufts possessed poorly vascularized pedicles. The picture was somewhat reminiscent of mesonephric glomeruli—hence the name "mesonephroma" (Fig. 5).

Teratocarcinomas. In 3 cases (1.7 per cent) carcinomas of the ovary were associated with teratomas. On gross examination they were single tumors with solid and cystic components. They tended to be hard, dense tumors. Microscopically, derivations of entoderm, ectoderm, and mesoderm arranged in a hodgepodge fashion with regions of carcinoma or sarcoma were seen (Fig. 6).

Hypernephroid carcinoma. Lesions of this type, apparent in 3 cases (1.7 per cent), had no pathognomonic gross features. Microscopically (Fig. 7), clear polygonal malignant cells were dispersed in a trabecular or pseudoalveolar pattern. Grouping in cell aggregates separated by coarse or fine strands of connective tissue and an intimate relation to sinusoidal and capillary blood spaces were characteristic. At times it was difficult to differentiate these tumors histologically from luteinized granulosa cell tumors, masculinovoblastomas, and metastatic hypernephroma. Clinical features were helpful in determining the type of tumor.

An attempt was made to correlate the clinical stage with the degree of malignancy as determined by Broders' method of grading (Table VI). It is readily apparent that in stage 4 the number of ovarian tumors of grades 3 and 4 is significantly high whereas in stages 1 and 2 there is a preponderance of low grade tumors (grades 1 and 2).

There was no positive correlation between histologic type of malignancy and clinical stage. There was almost equal distribution of each histologic type represented in each clinical stage.

TABLE VII.—FIVE YEAR SURVIVAL RATES BY PATHOLOGIC TYPE

	Patients		Lived 5 or more years after operation*	
	Total	Traced	No.	Per cent
Papillary serous cystadenocarcinoma	75	73	45	61.6
Seroanaplastic type adenocarcinoma	34	34	6	17.6
Mucous type cystadenocarcinoma	21	20	13	65.0
Endometrial type adenocarcinoma	19	19	13	68.4
Mesonephroma type adenocarcinoma	8	8	4	—
Mixed serous and mucinous type cystadenocarcinoma	4	4	4	—
Teratoma associated with carcinoma	3	3	1	—
Hypernephroid type	3	3	3	—
Total	167	164	89	54.3

*Based on traced patients. Inquiry as of January 1, 1956. Hospital deaths are excluded in the calculation of survival rates.

TABLE VIII.—FIVE YEAR SURVIVAL RATES BY GRADE OF MALIGNANCY

Grade of malignancy	Patients		Lived 5 or more years after operation	
	Total	Traced	No.	Per cent*
1	66	64	53	82.8
2	38	38	22	57.9
3 and 4	63	62	14	22.6
Total	167	164	89	54.3

*Based on traced patients. Inquiry as of January 1, 1956. Hospital deaths are excluded in the calculation of survival rates.

SURVIVAL

As mentioned previously, from January 1945 through December 1949 there were 172 patients with primary carcinoma of the ovary who underwent initial surgical procedures at the Mayo Clinic. Five patients died during the period of hospitalization and their cases have been excluded from the analysis. Follow-up information has been complete to date in 164 of the remaining 167 patients (98.2 per cent). Eighty-nine of the 164 traced patients (54.3 per cent) have survived 5 years or more.

The results were analyzed in an effort to correlate prognosis with histologic type, grade of malignancy, and clinical stage of involvement (Tables VII, VIII, and IX). The most favorable prognosis was found in the group of patients having endometrial type adenocarcinoma (68.4 per cent, 5 year survival rate); prognosis was poorest (17.6 per cent, 5 year survival rate) for the group having seroanaplastic adenocarcinomas. If

TABLE IX.—FIVE YEAR SURVIVAL RATES BY STAGE OF DEVELOPMENT

Stage of development	Patients		Lived 5 or more years after operation	
	Total	Traced	No.	Per cent*
1	39	38	35	92.1
2	35	34	30	88.2
3	50	50	22	44.0
4	43	42	2	4.8
Total	167	164	89	54.3

*Based on traced patients. Inquiry as of January 1, 1956. Hospital deaths are excluded in the calculation of survival rates.

TABLE X.—FIVE YEAR SURVIVAL RATES: SURGICAL TREATMENT WITH AND WITHOUT IRRADIATION

Treatment	Patients		Lived 5 or more years after operation	
	Total	Traced	No.	Per cent*
Surgical alone	72	71	46	64.8
Surgical with irradiation	95	93	43	46.2
Total	167	164	89	54.3

*Based on traced patients. Inquiry as of January 1, 1956. Hospital deaths are excluded in the calculation of survival rates.

the papillary serous cystadenocarcinomas are excluded from the analysis then 44 of 89 traced patients survived for 5 years or more, giving an over-all 5 year survival rate of 49.4 per cent.

When the survival rates were correlated with the grade of malignancy of the individual tumor, a progressive decrease in survival was noted for each higher grade of malignancy (Table VIII).

A definite correlation between clinical stage of involvement and prognosis was present (Table IX): 92.1 per cent of patients having stage 1 tumors survived 5 years, whereas, only 4.8 per cent of patients with tumors in stage 4 lived 5 years after operation.

Table X shows the results of patients treated by operation alone compared with those who received additional radiation therapy. These findings are in no way indicative of the value of irradiation, because the patients with the poorest prognosis were the ones receiving this additional therapy. Two facts are evident: (1) somewhat more than half of the patients in this series received radiation therapy, and (2) the 5 year survival rate for those patients

who did not have any x-ray therapy postoperatively was about 65 per cent.

COMMENT

The clinical findings in this group of patients agree in general with those of other reports in the literature. Several points, however, are worthy of comment.

The value of prophylactic removal of the ovaries at the time of pelvic operation for benign disease has been the subject of considerable discussion in the literature with a wide divergence of opinion being expressed. It is interesting to note in this regard that so-called prophylactic removal of the ovaries could have been justified in only 5 of the 26 patients in our series who had undergone previous abdominopelvic operations prior to the discovery of carcinoma, that is, if one considers 44 years of age as an arbitrary upper limit for preserving normal ovaries. Carcinoma subsequently developed in 1 of our patients when only a remnant of an ovary was left.

We would agree with Counseller and associates that each case should be considered individually as to whether or not ovarian function should be preserved. In young women desiring children a conservative operation may be done when the disease is localized, if the patient wishes to accept the risk of recurrent disease. This procedure is not to be encouraged, however, except in carefully selected cases. In women 45 years of age and older and those younger who will benefit from oophorectomy, we believe that so-called prophylactic removal of the ovaries is indicated.

Randall and Gerhardt, on the other hand, are of the opinion that the incidence of ovarian cancer does not justify the prophylactic removal of normal ovaries. As evidence of this point of view, they stated that the probability of development of carcinoma of the ovary is always less than 1 per cent and that the odds are never more than 9 chances in 1,000. Further, they stated that the probability decreases rapidly after 50 years of age. Their statistics are based on the incidence of carcinoma of the ovary as reported by physicians in upper New York state.

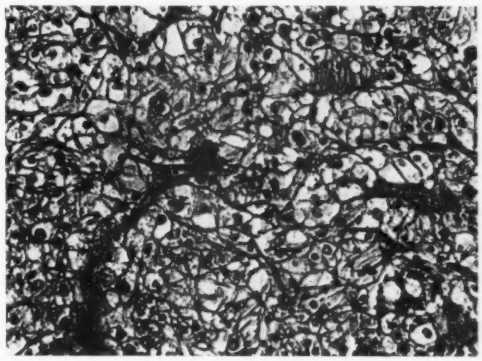

FIG. 7. Hypernephroid type of adenocarcinoma. Hematoxylin and eosin, ×141.

Corscaden, who considers the problem to be more philosophic than technical, wrote "It is just as impractical to have an idolatrous attitude toward the ovary as it is mischievous to remove these organs unnecessarily."

We were interested in determining the effect of accidental rupture of the cystic component of ovarian carcinoma on survival. It would appear that the clinical stage of disease at the time of exploration is the determining factor in survival, and that rupture of a malignant cyst is of secondary importance. Data in favor of this opinion showed that patients in whom the cystic component was ruptured at the time of operation survived longer if the disease was localized than if extensive malignant involvement was present. This finding admittedly is based on a small number of cases, but it agrees with the findings of Cariker and Dockerty, who found that the accidental rupture of a malignant mucinous type ovarian carcinoma did not affect the prognosis adversely.

The over-all relative survival rate of 54.3 per cent is most gratifying. A review of the literature revealed a marked inconsistency in reported survival rates ranging from 14.5 to 36.4 per cent with perhaps an average 5

year survival rate of 15 to 20 per cent. Explanation of this variation lies mainly in the criteria for making a pathologic diagnosis of carcinoma of the ovary.

In a study of this type it is impossible to draw any valid statistical conclusions from the data as to the value of radiation therapy in the treatment of carcinoma of the ovary. However, it is our opinion that radiation therapy has a definite place in the treatment of patients having ovarian cancer of advanced grades, chiefly to prolong survival time and perhaps, occasionally, to cure residual disease. Certainly, the 5 year survival rate of 4.8 per cent for patients having stage 4 lesions is evidence in favor of this opinion.

SUMMARY AND CONCLUSION

A clinicopathologic study of 172 cases of primary carcinoma of the ovary encountered at the Mayo Clinic during the 5 year period 1945 through 1949 has been presented. The peak age incidence was in the sixth decade and the commonest symptoms were abdominal pain and swelling.

The relative over-all 5 year survival rate was 54.3 per cent. When the papillary serous cystadenocarcinomas were excluded from the analysis the over-all 5 year survival rate was 49.4 per cent.

Prognosis depends chiefly on the histologic type of tumor and on the histologic degree of malignancy, both of which control, to a large degree, the clinical extent of the disease. Patients having ovarian tumors of low grade malignancy have the most favorable prognosis (82.8 per cent, 5 year survival rate for patients having grade 1 malignant lesions). Similarly, tumors confined to the adnexa react most favorably to treatment.

The clinical extent of the disease at the time of exploration seems to be the determining factor in survival when the cystic component of the ovarian carcinoma is ruptured at the time of surgical removal.

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ESOPHAGEAL REPLACEMENT AND BYPASS WITH THE ASCENDING AND RIGHT HALF OF THE TRANSVERSE COLON FOR THE TREATMENT OF CONGENITAL ATRESIA OF THE ESOPHAGUS

J. STANLEY BATTERSBY, M.D., F.A.C.S., and THOMAS C. MOORE, M.D., F.A.C.S.,
Indianapolis, Indiana

ALTHOUGH the great majority of cases of congenital atresia of the esophagus may be managed by primary end-to-end esophageal reconstruction, a few cases occur in which esophageal substitution is necessary. While substitution seldom is required in most cases of esophageal atresia with tracheo-esophageal fistula, it is needed in virtually all cases of the infrequently encountered atresias without fistula because of the high incidence in this group of partial or complete absence of the distal esophageal segment. Until recently, the results with the use of a variety of methods of esophageal substitution in these cases had been disappointing. However, encouraging initial experiences with the use of detached segments of right half of the colon[1] on a suitable vascular pedicle suggest that a workable solution to this difficult problem may be near at hand.

The use of colon for esophageal replacement and bypass is not new. The literature relating to the problem of esophageal substitution was reviewed in detail in 1934 by Ochsner and Owens and more recently by Mahoney and Sherman. A detached segment of colon, the transverse, was first used for esophageal substitution by Kelling in 1911. Roith, in 1923, reported the use of the right half of the colon for esophageal replacement. The earliest successful use of colon for esophageal substitution in childhood was recorded in 1921 by Lundblad(5). He employed transverse colon for esophageal replacement in a 3 year old boy who had a corrosive stricture of the esophagus. A 15 year follow-up study of this patient was reported by him in 1934(6). He found that the esophagus had grown with the child and had functioned satisfactorily.

Sandblom, in 1948, reported an attempt to use colon for esophageal replacement in a patient with congenital atresia of the esophagus. His patient was a 2 day old girl who had an esophageal atresia with tracheo-esophageal fistula. The distance between the two esophageal segments was too great for a primary end-to-end anastomosis. He attempted to use transverse colon for intrathoracic esophageal replacement. However, cardiac arrest occurred shortly after the completion of the proximal esophagocolic anastomosis and the infant expired. The first successful experience with the use of colon in esophageal atresia was recorded in 1954 by Javid. His patient had a tracheo-esophageal fistula and had been managed by ligation of the fistula, gastrostomy, and an esophagostomy in the neck at birth. Esophageal replacement with the right half of the colon was carried out at 18 months of age through a subcutaneous tunnel in front of the sternum.

Because of the limited published experience with the use of the right half of the colon for esophageal replacement in the

From the Department of Surgery, Indiana University Medical Center, Indianapolis, Indiana.
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[1]The ascending and right half of the transverse colon will be designated as the right half of the colon in this article.

FIG. 1.

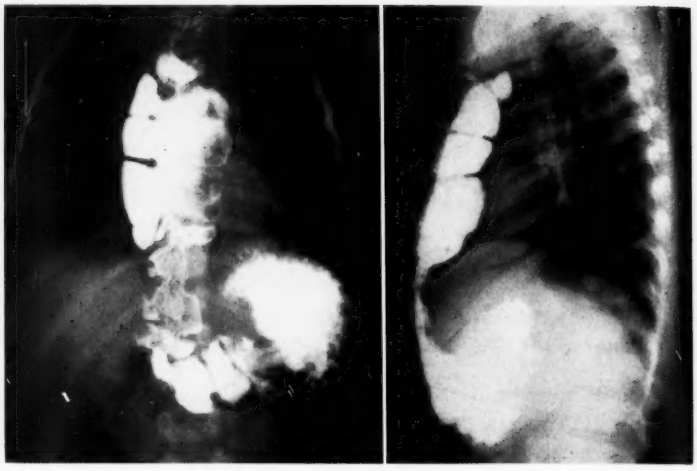

FIG. 2.

FIG. 1. Photograph of patient in Case 1 just prior to esophageal substitution with substernal right half of colon at 9 months of age.

FIG. 2. Posteroanterior and lateral roentgenograms in Case 1 after barium swallow showing satisfactory function of substernal right half of colon as esophageal substitute 5 years after operation.

management of congenital atresia of the esophagus, it has seemed desirable to record our experience at the Indiana University Medical Center in 5 cases. Four of the patients had esophageal atresia, no fistula, and absence of the distal esophageal segment, and 1 had atresia with tracheo-esophageal fistula. In the first successful case in this series, the patient was operated upon in January of 1953. This patient is alive and doing well almost 6 years following operation.

CASE REPORTS

CASE 1. T. P., a 36 hour old white male infant, was admitted to the Indiana University Medical Center on April 12, 1952 with a tentative diagnosis of esophageal atresia with tracheo-esophageal fistula. His birth weight had been just 5 pounds. Roentgenographic study on admission demonstrated obstruction to the passage of an opaque rubber catheter at the level of the second dorsal vertebra and the presence of gas in the gastrointestinal tract. He was taken to the operating room on April 13. The area of the esophageal atresia and tracheo-esophageal fistula was exposed by means of a retropleural dissection. The tracheo-esophageal fistula was divided and the tracheal end was ligated. Both the proximal and distal esophageal segments were freed upward. There was not enough esophageal length for the two ends to meet. The open end of the distal esophageal segment was closed, and the operation was terminated by closure of the incision. Two days later, on April 15, the upper part of the abdomen was opened and a Roux-Y jejunal limb was created. The Roux-Y jejunal segment was brought subcutaneously from the area of the xiphoid to an incision in the lower left cervical region. The operation was completed with a Stamm gastrostomy for feeding purposes. However, it soon became apparent that the jejunal limb had become ischemic, and, on April 19, the gangrenous jejunal limb was removed from the subcutaneous tunnel and was resected. The open end of the Roux-Y jejunal remnant was left in the epigastrium near the xiphoid for drainage. An esophagostomy was performed in the left lower part of the neck at this time. The patient recovered from these procedures and gained weight satisfactorily on gastrostomy feedings. He was discharged from the hospital on May 4. The open end of the Roux-Y jejunal segment was closed on June 30 during a readmission to the hospital for this purpose.

The patient continued to grow and develop satisfactorily on stoma feedings. He was admitted to the hospital on January 19, 1953, at 9 months of age, for

esophageal reconstruction with the right half of the colon. He appeared well nourished at this time and weighed 19 pounds and 12 ounces (Fig. 1). Neomycin was given through the gastrostomy opening prior to operation. He was taken to the operating room on January 24, and the right half of the colon was mobilized through an abdominal incision. The intestine was divided at the ileocecal junction and at the transverse colon just distal to the middle colic artery. Adequate blood supply to the right half of the colon through the middle colic artery was demonstrated and the right colic and ileocolic arteries were divided and ligated. The cecal end of the mobilized right half of the colon could be brought up to the neck area without difficulty. The sternum was divided from the xiphoid to the sternal notch and the mobilized colon was placed in the anterior mediastinum. The divided sternum was reapproximated. The appendix was removed, the ileal stump was closed, and the cecum was anastomosed to the esophagus in the lower part of the neck on the left side in two layers with interrupted No. 5-0 silk sutures. The distal end of the mobilized colonic segment was anastomosed to the anterior wall of the stomach. Intestinal continuity was re-established by means of side-to-side anastomosis between the ileum and the distal portion of the transverse colon. The procedure was tolerated satisfactorily and gastrostomy feedings were started 3 days after operation. The postoperative course was complicated by the occurrence of a fistula in the lower part of the neck on the left side 5 days after operation. There was some diarrhea in the early postoperative period. He was discharged from the hospital on March 13. The fistula drained for 4 months and then remained closed.

Approximately 7 months after operation, some difficulty with swallowing was found to be due to constriction of the colon where it passed through the diaphragm. This difficulty became progressively worse until March 27, 1954 when a plastic procedure was carried out to enlarge the diaphragmatic hiatus through which the colon passed. The gastrostomy opening was closed by operation on January 19, 1956. Roentgenographic study of the colon transplant in January of 1958 showed satisfactory passage, without delay, of the barium into the stomach (Fig. 2). Some difficulty with more solid foods in late November 1958 was associated with an inconstant, temporary delay in the passage of barium at the esophagocolic anastomosis on fluoroscopic study. At times no delay whatsoever could be detected. It is possible that some degree of stricture may be developing at the level of the esophagocolic anastomosis. He has continued to grow and develop normally. His health and nutrition were good, when he was seen last, nearly 6 years after esophageal reconstruction with right half of the colon (Fig. 3).

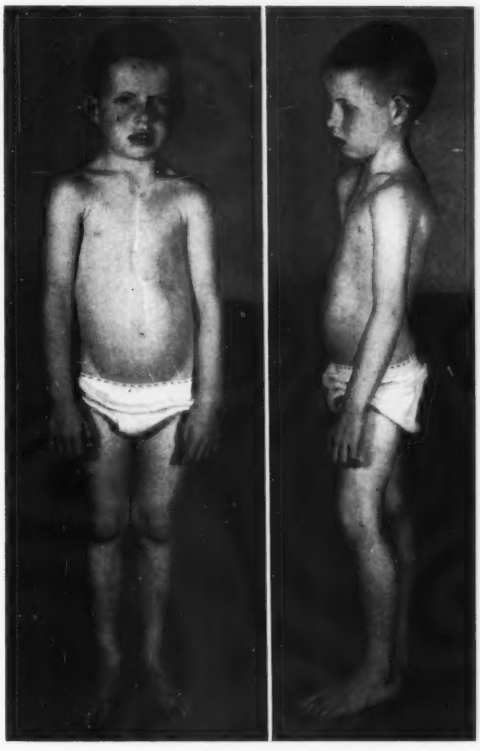

FIG. 3. Appearance of patient in Case 1 nearly 6 years after esophageal replacement with right half of colon.

CASE 2. M. P., a 3 day old premature white female infant, was admitted to the Indiana University Medical Center on April 7, 1954, with a diagnosis of esophageal atresia without fistula. A gastrostomy had been performed on the day prior to admission, following roentgenographic demonstration of esophageal atresia and the absence of gas in the gastrointestinal tract. She weighed 4 pounds and 11 ounces at birth. Gastrostomy feedings were started shortly after the patient was admitted to the hospital and salivary secretions were removed from the upper esophageal segment by intermittent aspiration. Neomycin was given the gastric stoma for 2 days prior to operation. The patient was taken to the operating room on April 12. She weighed 4 pounds and 8 ounces at this time. The right fifth rib was removed subperieosteally, and the mediastinum was exposed by retropleural dissection. The upper esophageal segment ended blindly at approximately the level of the second dorsal vertebra. The lower esophageal segment was virtually nonexistent. It measured less than 1 centimeter in length. The peritoneal cavity was opened through an abdominal incision. The right half of the colon was mobilized. The distal portion of the ileum and the midtransverse segment of the colon were transected. The appendix was removed and the ileum

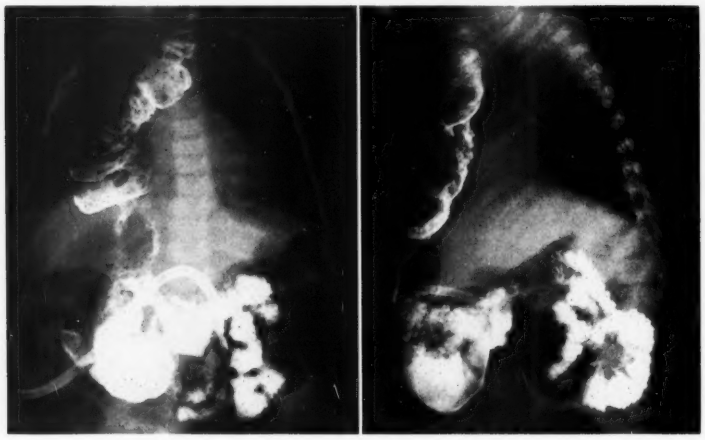

FIG. 4.

FIG. 4. Case 3. Roentgenograms after barium swallow showing appearance of substernal right half of colon 1 year after operation.

FIG. 5. Case 5. Photograph of patient demonstrating good nutrition and normal development 17 months after the use of substernal right half of colon for esophageal replacement.

FIG. 5.

was closed at the ileocecal area. The proximal end of the mobilized right half of the colon was brought into the right side of the chest through an opening which was made in the diaphragm anterior and to the right of the hilus of the liver. The upper esophageal pouch was dissected free and was anchored to the cecum with interrupted sutures of No. 5-0 silk. The esophagus and cecum were opened and the anastomosis was carried out in one layer with interrupted sutures of No. 5-0 arterial silk. The ileum and the distal segment of transverse colon were united by an oblique end-to-end anastomosis. The distal end of the mobilized right half of the colon was brought out through the abdominal incision as a colostomy opening. The operation was tolerated satisfactorily and gastrostomy feedings were resumed on the day following operation.

Four days after operation, on April 17, the gastric stoma was eliminated and the distal end of the mobilized right half of the colon was anastomosed to the anterior surface of the stomach. A new gastrostomy opening was created. Gastrostomy feedings again were given on the day after operation. Oral feedings were started 3 days later. She appeared to be doing well in the early postoperative period. She took her feedings well both orally and through the gastrostomy tube, and passed soft formed stools at regular intervals. However, a slow but progressive loss of weight was noted. Her weight had fallen to 3 pounds and 12 ounces by April 30. Several small cutaneous abscesses were found on her body at this time. Respiratory distress and abdominal distention appeared rather suddenly on May 1. Her condition deteriorated rapidly and she died in a matter of hours. Permission for postmortem examination was not granted.

CASE 3. O. N., a 4 year old white male, was admitted to the Indiana University Medical Center on September 19, 1956, for elective esophageal reconstruction with right half of the colon. He had been born with an esophageal atresia without fistula and had been operated upon at the University of Michigan Hospital shortly after birth. A gastrostomy for feeding purposes and an esophagostomy in the neck had been carried out. He had suffered from repeated episodes of respiratory tract infection in the intervening years and his state of nutrition had remained poor.

On admission to the hospital, the patient was found to be a frail child with evidence of marked retardation of growth. He weighed 17 pounds and 5 ounces. Neomycin was used for gastrointestinal preparation prior to operation. He was taken to the operating room on September 28. A right rectus abdominal incision was employed and the right half of the colon was mobilized. The ileum was divided 12 centimeters from the ileocecal valve. The right colic and ileocolic arteries were ligated. A substernal tunnel was created by blunt dissection and the right half of colon with ileum was brought through the tunnel to an incision in the lower part of the neck on the left side. The appendix and a portion of ileum were removed. Approximately 6 centimeters of ileum remained, and

a two layer anastomosis was carried out between the ileum and the freed proximal esophagus. The sternal head of the sternocleidomastoid muscle, the head of the clavicle, and the adjacent portion of the first rib were resected to provide adequate room for the cecum in this area. The gastric stoma was removed for technical reasons and the transverse colon was divided just distal to the level of the middle colic artery. The distal end of the segment of right half of the colon was anastomosed to the anterior wall of the stomach. Intestinal continuity was re-established by an oblique end-to-end anastomosis between the ileum and the transverse colon, and a new gastrostoma was created. The patient was returned to the ward in good condition. Oral feedings were started 4 days after operation. The postoperative course was uncomplicated. The patient was eating a soft diet and was gaining weight steadily by the time of his discharge from the hospital on November 4. He was readmitted to the hospital on July 30, 1957 for follow-up studies. He weighed 29 pounds. His appetite was good and he had started to walk. Roentgenographic studies revealed that barium taken by mouth passed through the substernal colonic tube and entered the stomach in the antral region without delay (Fig. 4). He has done well and eats without difficulty.

CASE 4. A. T., a premature white female infant, was born at the Indiana University Medical Center on June 19, 1956. Her weight at birth was 4 pounds and 11 ounces. The pregnancy had been complicated by the occurrence of polyhydramnios. Roentgenographic study of the chest revealed the presence of esophageal atresia without tracheo-esophageal fistula. A Stamm gastrostomy was carried out on June 20. An attempt at roentgenographic study of the upper gastrointestinal tract with barium injected through the gastrostomy tube on June 21 resulted in the accidental extrusion of a large amount of barium into the peritoneal cavity. Laparotomy was performed promptly to remove the barium and to reconstruct the gastric stoma. The patient recovered satisfactorily and 9 days later was returned to the operating room for an exploratory thoracotomy on the right side to determine the status of the two esophageal segments. The proximal esophageal segment ended blindly and was found to be approximately 1 centimeter longer than the usual length of the proximal segment. The distal esophageal segment was absent. An esophagostomy opening for the proximal segment was created in the back by means of an indwelling catheter at the level of the atresia. This was done in an effort to maintain as much length of proximal esophagus as possible for subsequent reconstruction within the chest. She continued to be maintained by gastrostomy feedings following operation and was released from the hospital on September 22. She was readmitted to the hospital for revision of a stenotic esophagostomy opening on October 20. She weighed 7 pounds and 4 ounces at this time.

She was admitted to the hospital at 6 months of age on January 14, 1957, for elective reconstruction of the esophagus. She weighed 9 pounds and 10 ounces. Sulfasuxidine was employed for intestinal preparation. She was taken to the operating room on January 18. The peritoneal cavity was entered. Numerous adhesions were found to have occurred in the wake of the barium peritonitis, and they interfered significantly with the mobilization of the right half of the colon. Adequate blood supply to the right half of the colon from the middle colic artery could be demonstrated by occlusion and then division of the ileocolic artery. There was no well defined right colic artery. The terminal ileum was divided and the appendix was removed. The old thoracotomy incision on the right side was reopened and the distal end of the proximal esophageal segment was dissected free. The diaphragm was opened with a stellate incision anterior to the suspensory ligament of the liver. The freed right half of the colon with terminal ileum was brought through this opening in the diaphragm into the right side of the chest. The anastomosis was carried out in the right side of the chest between esophagus and ileum. An outer row of interrupted No. 5-0 silk sutures and an inner row of interrupted No. 6-0 catgut sutures were utilized. The transverse colon was divided distal to the middle colic artery. Intestinal continuity was re-established by an oblique end-to-end anastomosis between the distal part of the ileum and the transverse colon. The proximal end of the divided transverse colon was anastomosed to the anterior wall of the stomach. The gastrostoma was not altered because of the dense adhesions which had occurred about it.

She tolerated the operation well and her early postoperative course was uneventful. Oral feedings were started 5 days postoperatively, following roentgenographic demonstration of an intact esophagoileal anastomosis. Her progress was satisfactory until 11 days following operation when her condition suddenly deteriorated with evidence of an anastomotic breakdown within the right side of the chest. At this time a thoracostomy tube was inserted into the right side of the chest through the bed of short segment of rib resected under local anesthesia. A large amount of formula was encountered in the right pleural space. Nonetheless, her condition continued to be poor and she expired on February 6, 19 days following the esophageal reconstruction. Permission for postmortem examination was not granted.

CASE 5. P. F., a 2 day old white female infant, was admitted to the Indiana University Medical Center on November 3, 1956, with a diagnosis of esophageal atresia without fistula. The patient had been born at the termination of a full term pregnancy and weighed 6 pounds and 14 ounces at birth. There was no evidence of gas in the gastrointestinal tract on roentgenographic study of the abdomen. On November 4, the patient was taken to the operating room and an

TABLE I.—SUMMARY OF PUBLISHED EXPERIENCE WITH USE OF COLON FOR ESOPHAGEAL REPLACEMENT IN CASES OF CONGENITAL ATRESIA OF THE ESOPHAGUS

Author	*Date of report*	*Nature of defect*	*Date of operation*	*Age of child at operation*	*Weight of child at operation, pounds*	*Segment of colon used*	*Position of colon*	*Result*	*Remarks*
Javid	1954	Atresia with fistula	6–10–53	18 months		Right half	Subcutaneous	Recovered	Two stages 6 weeks apart. Ileum to esophagus in neck. Fistula at anastomosis in neck healed spontaneously. Follow-up of 5 months. Doing well
Dale and Sherman									
Case 1	1955	Atresia with fistula	1–22–54	30 months	21	Right half	Substernal	Recovered	One stage. Cecum to esophagus in neck. Fistula at anastomosis in neck. Healed spontaneously but stricture developed requiring reoperation 5 months later. Follow-up of 9 months. Doing well
Case 2	1955	Atresia with fistula	4–23–54	21 months	16½	Right half	Substernal	Recovered	One stage. Cecum to esophagus in neck. No fistula. Follow-up of 5 months. Doing well
Nadal and Gustavson	1957	Atresia with fistula	8–1–55	25 months	26½	Right half	Substernal	Recovered	One stage. Cecum to esophagus in neck. No fistula. Follow-up of 10 months. Doing well
Sherman and Waterston	1957	Atresia without fistula	6–7–53	6 months		Transverse	Left intrathoracic	Recovered	Three stages during a period of 10 weeks. Colon to esophagus in neck. Two later operations to reduce and repair herniation of stomach through opening in diaphragm. No neck fistula. Follow-up of 3 years. Doing well
Battersby and Moore									
Case 1		Atresia with fistula	1–24–53	9 months	19	Right half	Substernal	Recovered	One stage. Cecum to esophagus in neck. Fistula at anastomosis in neck. Healed spontaneously. Operation for relief of stricture at diaphragm after 14 months. Follow-up of 6 years. Doing well. Some trouble swallowing bulk foods
Case 2		Atresia without fistula	4–12–54	8 days	4½	Right half	Right intrathoracic	Died	Two stages 4 days apart. Cecum to esophagus in chest. Oral feeding but progressive weight loss. Died 18 days following operation. No autopsy
Case 3		Atresia without fistula	9–28–56	4 years	17	Right half	Substernal	Recovered	One stage. Ileum to esophagus in neck. No fistula. Follow-up of 2 years. Doing well
Case 4		Atresia without fistula	1–18–57	6 months	9½	Right half	Right intrathoracic	Died	One stage. Ileum to esophagus in chest. Disruption of an anastomosis in chest 11 days after operation with death 8 days later. No autopsy
Case 5		Atresia without fistula	6–7–57	7 months	16	Right half	Substernal	Recovered	One stage. Cecum to esophagus in neck. Neck abscess drained. No fistula. Operation for relief of stricture at diaphragm after 2 months. Follow-up of 17 months. Doing well. Some trouble swallowing bulk foods

esophagostomy was performed in the inferior portion of the left side of the neck. At the same time, a Stamm gastrostomy also was carried out, but with some technical difficulty due to the extremely small size of the stomach. She did well with the gastrostomy feedings and weighed 7 pounds and 6 ounces at the time that she was discharged from the hospital on December 2.

She was readmitted to the hospital on June 3, 1957, at 7 months of age for esophageal reconstruction. At this time she weighed 16 pounds and 4 ounces. Sulfasuxidine was used for preoperative preparation of the intestine. Esophageal reconstruction with right half of the colon was carried out on June 7. The right half of the colon was mobilized. The ileocolic artery was occluded and then ligated following the demonstration of adequate arterial blood supply to the right half of the colon from the middle colic artery. The terminal ileum and transverse colon were transected. The esophagostoma was freed upward and a substernal tunnel was created by blunt dissection from the xiphoid to the sternal notch. The cecal end of the mobilized right half of the colon was brought into the neck through this tunnel by means of traction sutures. The appendix was removed and the ileum closed at its junction with the cecum. It was necessary to excise the sternoclavicular joint and the clavicular head to provide ample room for the cecum. The esophagus was anastomosed to the cecum. The gastric stoma was removed for technical reasons and the distal end of the substernal portion of colon was anastomosed to the anterior wall of the stomach. A new gastrostomy then was performed. Intestinal continuity was re-established by an anastomosis between the terminal part of ileum and the distal segment of transverse colon. The procedure was tolerated well by the patient and gastrostomy feedings were started 3 days following operation. A dehiscence of the abdominal wound occurred 7 days after operation and was closed in one layer with wire sutures. A small abscess developed in the neck incision 2 weeks after operation and was drained. However, no fistula formed in this area. She was released from the hospital on July 1.

Some difficulty with swallowing developed following her discharge. Roentgenographic studies demonstrated significant narrowing of the colonic tube at the level of the diaphragm. On August 9, abdominal exploration was carried out and the stenotic area where the colon passed through the diaphragm was enlarged by a stellate incision in the diaphragm. The anastomosis between the colon and the stomach also was enlarged.

She experienced some difficulty in learning how to take oral feedings, especially the more solid and bulky type of foods. However, with the passage of time she has had less and less difficulty. Her growth and development have continued to be normal (Fig. 5). She weighed 28 pounds in November of 1958.

DISCUSSION

Three of the 5 patients in this series recovered and are still living and doing well. The longest period of follow-up study is about 6 years. Both fatalities occurred in small and undernourished infants. They weighed 4½ and 9½ pounds and were operated upon at 8 days and 6 months of age respectively. In both of these cases intrathoracic esophageal anastomoses were carried out. All other anastomoses were performed in the neck with the colon being brought through a substernal tunnel. In 1 of the cases of intrathoracic anastomosis, the anastomosis was shown to have broken down and, in the other, anastomotic disruption was strongly suspected. The postoperative period of 1 of the 3 surviving patients was complicated by the occurrence of a fistula at the anastomotic site in the neck. The fistula drained for 4 months prior to spontaneous closure. An abscess in the area of the neck anastomosis was found 2 weeks following operation in another case. It was drained satisfactorily and no fistula formed. Operation for stricture in the area of the neck anastomosis has not been necessary in any of the patients. However, some difficulty with temporary retention of more solid foods in the area of the neck anastomosis has occurred in 2 patients. Narrowing at the site of colon passage through the diaphragm developed in 2 cases, requiring secondary operations to enlarge the artificially created diaphragmatic hiatus. Cruciate incisions in the diaphragm were utilized in both cases in the secondary operations and no further trouble has occurred. Resection of the sternoclavicular joint and the head of the clavicle was performed in 2 cases to provide greater room for the passage of the colon transplant from the substernal tunnel into the neck. The cecum was used for esophageal anastomosis in 3 cases, and the ileum was employed in 2.

Sherman and Waterston, in 1957, stated that 4 patients had been operated upon by the method of Waterston with only 1 death. His method involved esophageal replace-

ment with transverse colon in 3 stages. The first patient had been operated upon in September of 1951. Only 1 of these cases was reported in detail. They suggested oral feedings with drainage through the neck esophagostoma, as well as gastrostoma feedings, in the period prior to the use of colon for esophageal replacement in order to enable the infants to learn to swallow with greater ease after the colon transplant.

Haight, in 1957, summarized his experience with the use of colon transplants in 8 cases of esophageal atresia. Seven of the patients survived. Their ages at the time of reconstruction ranged from 2½ to 7½ years. A leak at the cervical anastomosis occurred in 2 patients, and in 2 others strictures of the cervical anastomosis subsequently developed. The cervical anastomosis of 1 patient had to be opened elsewhere for decompression. Intestinal obstruction occurred 3 weeks postoperatively in 1. The details of the individual cases and the periods of follow-up study were not given.

Only 5 cases have been recorded in the literature in sufficient detail to be suitable for analysis. The findings in these cases are summarized in Table I, along with the 5 cases recorded for the first time here. The best results were achieved in infants and children in good nutritional status who were operated on at 6 months of age or older. The one stage operation in which the right half of colon was used through a substernal tunnel was popular and gave best results.

It would appear that the infant with atresia and esophageal fistula and inadequate length of esophagus for primary end-to-end anastomosis should be managed initially by ligation of the fistula and by a gastrostomy and an esophagostomy in the neck. Nutrition may be maintained by gastrostoma feedings. Esophageal reconstruction with right half of colon should be deferred, if possible, until the infant is past 6 months of age and 15 pounds in weight. The newborn infant with esophageal atresia and no air in the stomach on roentgenographic study may be presumed, in all likelihood, to have no fistula. Due to the high incidence of inadequate distal esophageal segments in these cases, these infants are best managed initially by esophagostomy in the neck and gastrostomy for feeding with esophageal reconstruction being deferred until later. The status of the distal esophageal segment in these cases may be evaluated later through the gastrostomy as suggested by Haight.

Esophageal anastomosis with either cecum or ileum in the neck seemed to be safer than when carried out within the chest. This was due largely to the relatively high incidence of leakage and fistula formation at the site of these anastomoses. A fistula in the neck occurred in 3 of the 8 cases in which esophageal anastomosis was carried out in the neck. In an additional case, an abscess without fistula developed in the area of the neck anastomosis. A breakdown of the intrathoracic esophageal anastomosis was established in one case and was strongly suspected in the other. Both of these patients died. All of the patients with neck fistulas recovered and the fistulas all healed spontaneously within a period of several weeks.

Peptic ulceration of the colon transplant was not observed in any of the recorded cases. The longest period of follow-up observation has been almost 6 years. This greater resistance of the colon to peptic ulceration and the relatively greater lengths of intestine which can be mobilized for esophageal replacement would appear to justify more frequent utilization of right half of colon in those cases of congenital atresia of the esophagus in which esophageal substitution is necessary.

SUMMARY

1. The literature pertaining to the use of right half of colon for esophageal replacement in the management of congenital atresia of the esophagus is reviewed.

2. A need for esophageal replacement exists in the infrequent case of esophageal atresia with tracheo-esophageal fistula in which there is insufficient length of the two esophageal segments for primary end-to-

end anastomosis and in virtually all cases of the rather small group of atresias without fistula in which the distal esophageal segment generally is partially or completely absent. The initial management of these two types of cases at birth is discussed.

3. The use of right half of the colon for esophageal replacement in 5 cases of congenital atresia of the esophagus is reported. There was esophageal atresia without fistula and with absence of the distal esophageal segment in 4 cases and atresia with tracheoesophageal fistula in 1.

4. The cecum was utilized for proximal esophageal anastomosis in 3 cases and the terminal part of the ileum in 2. All distal colonic transplant anastomoses were carried out into the anterior wall of the stomach. The substernal route with esophageal anastomosis in the neck was used in 3 cases, and intrathoracic colon transplantation with intrathoracic esophageal anastomosis was employed in 2.

5. Three patients recovered and 2 died. The 3 surviving patients were all in excess of 7 months in age and 16 pounds in weight at the time of operation. The substernal route with esophageal anastomosis in the neck was utilized in all 3. The surviving patients have been observed for 6, 2, and 1¾ years after esophageal replacement. The transplanted right half of colon has functioned satisfactorily as an esophageal substitute in all, and they have grown and developed in a normal manner. There has been no evidence of peptic ulceration in the colon transplant.

6. Both infants died who were managed by intrathoracic right half of colon esophageal replacement with the esophageal anastomosis in the chest. One patient, a 4½ pound premature infant, was operated upon at 8 days of age and died 18 days following operation with progressive loss of weight and suspected terminal intrathoracic anastomosis breakdown. The other patient was a malnourished 6 months old infant who weighed only 9½ pounds. This patient died 8 days after a breakdown of the intrathoracic anastomosis which occurred 11 days following operation.

7. Leakage with the formation of a fistula at the proximal esophageal anastomosis was the most frequently encountered postoperative complication.

8. In those cases of congenital atresia of the esophagus in which esophageal replacement is required, the use of the right half of the colon through a substernal tunnel with proximal esophageal anastomosis in the neck is recommended. The advantages of the use of the right half of the colon are discussed. It is suggested that esophageal reconstruction be deferred until the patient is past 9 months of age and in good nutrition.

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THE INFLUENCE OF TEMPERATURE AND CORONARY OCCLUSION ON THE VENTRICULAR FIBRILLATION THRESHOLD

CLIFFORD M. PHIBBS, M.D., LOUIS M. LEVY, B.S., and
LLOYD D. MacLEAN, M.D., Ph.D., St. Paul, Minnesota

THE IMPRESSION has existed for many years that physiologic, physical, and chemical influences can create a propensity to, or resistance against, ventricular fibrillation. Wiggers (6) pointed out in 1940 that any quantitative knowledge of the likelihood of these influences causing ventricular fibrillation or protecting against it depends upon measurement of ventricular fibrillation thresholds. The great variation in the fibrillation time or mortality rate following acute coronary occlusion is well known. It is possible to select three groups of dogs in the same laboratory and to ligate the anterior descending ramus of the left coronary artery and to obtain an incidence of ventricular fibrillation that is quite different in all groups. One could easily be deluded into believing that an antifibrillatory agent or cardiac revascularization operation was effective under these circumstances. The replacement of this bio-assay technique by modern electronic instrumentation combined with threshold measurements affords one the opportunity to measure the degree of change an influence has induced. The concept of measuring fibrillation thresholds introduced by Wiggers has been further studied, improved, and applied by Brooks, Hoffman, Suckling, and Orias and by Shumway, Johnson, and Stish.

The present investigation uses these techniques to quantitate the effects of hypothermia and hyperthermia upon ventricular fibrillation threshold in the dog and monkey heart. It is generally agreed that hypothermia greatly increases the chance of ventricular fibrillation in the human and dog heart and coronary occlusion is poorly tolerated in this state. Few attempts have been made to assay the effects of hyperthermia on cardiac excitability.

From the Ancker Hospital Surgical Research Laboratory, St. Paul, and Department of Surgery, University of Minnesota, Minneapolis, Minnesota.
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METHODS

This investigation was performed on adult mongrel dogs of either sex, weighing between 12.5 and 19 kilograms, and on rhesus monkeys. Following intravenous pentobarbital anesthesia, 30 milligrams per kilogram, the heart was exposed through a left thoracotomy in the fifth intercostal space. All animals were ventilated with compressed room air using an electronic respirator. The duration of experiments was 6 to 12 hours. Additional anesthesia was given in small increments of 25 to 50 milligrams intravenously. The minor alterations in depth of anesthesia that occurred throughout these experiments did not influence ventricular fibrillation thresholds. The esophageal, rectal, and cardiac temperatures were measured in all dogs and did not vary by more than 1 degree C. The cardiac temperature was measured by a thermistor mounted in a 20 gauge needle, the rectal and esophageal temperatures by an electronic thermometer. It was found that the esophageal temperature was the most reliable as stool in the rectum can cause an erroneous reading if this measurement alone is relied upon.

The pericardium was incised longitudinally and all thresholds were determined on the left ventricle. The precise area where the threshold stimulus was applied was recorded for each experiment.

The instrumentation used was similar to that described by Shumway, Johnson and Stish. Amplified electrocardiogram potentials were fed into a triggering circuit, the output of which was coupled to the synchronizing input of a Grass stimulator. The output of the stimulator was connected to a bipolar electrode. One lead of the electrode contained a 5,000 ohm resistor to minimize the effects of changing resistances between the electrodes and cardiac surface. Two oscilloscopes were used. On one the electrocardiogram was displayed. The stimulator output was applied to this oscilloscope so that brightening of the trace at the moment of stimulation provided a direct method of determining precisely the location of the stimulus in the cardiac cycle. The other oscilloscope was used to determine the magnitude in milliamperes of the current delivered. The trigger circuit provided a single synchronizing pulse for the stimulator upon the occurrence of the first R wave after the trigger button was released. A wide range of stimulus strength, duration, and delay were provided by the stimulator. A stimulus duration of 10 milliseconds was used in all testing. In all animals studied an initial ventricular fibrillation threshold was determined at normothermia by sweeping the vulnerable period (terminal 30 to 90 milliseconds of systole) of the cardiac cycle with stimuli of increasing current strength from subthreshold to threshold levels. The criterion of threshold was persistent ventricular fibrillation.

The delay setting of the stimulator, which could be varied, was helpful in allowing accurate sweeping of the cardiac cycle. The delay period, which determined precisely the location in the cardiac cycle when the stimulus was delivered, was measured from the R wave in the QRS complex. A single stimulus was applied to the heart beginning shortly after the QRS complex and was repeated in subsequent cardiac cycles throughout the vulnerable period, and beyond, by progressively increasing the delay in time from the R wave 5 milliseconds after each stimulus. Only a single stimulus was applied to each cardiac complex tested. At least 2 or 3 normal heart beats were allowed to elapse between each stimulus.

Since the duration of stimulus was 10 milliseconds and the delay from the R wave was increased at 5 millisecond increments we could deliver stimuli to the heart before, during, and following the entire vulnerable period. Thus, if the pulse rate were to change or the vulnerable period were to expand or contract as a result of an influence such as temperature alteration, we were assured of delivering a standard stimulus of 10 milliseconds' duration to any potentially vulnerable time in the cardiac cycle.

After sweeping the entire vulnerable area at one subthreshold strength, the procedure was repeated after increasing the current strength by from 1.0 to 1.5 milliamperes. This was repeated until ventricular fibrillation was produced at which time the location in the cardiac cycle, the location on the heart surface, and the strength of stimulus were recorded.

The instrumentation provides a single square wave stimulus of known strength and known duration which can be delivered at a known, measurable and alterable time in the cardiac cycle and which is applied to a known area on the heart surface.

After accomplishing fibrillation by this test procedure, defibrillation was accomplished quickly, usually in less than 10 seconds, using standard equipment. After a 5 to 10 minute rest period when the electrocardiogram had returned to normal further tests were run with confidence that the fibrillation threshold was not altered.

All animals were heated using a hypohyperthermia unit. Cooling was accomplished with the same device or by immersing the animal in an ice water bath. Blood samples were obtained throughout the ex-

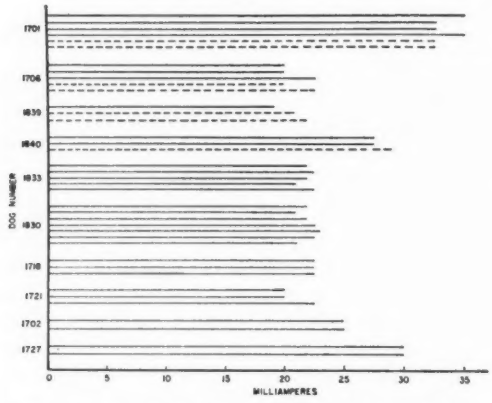

FIG. 1. Ventricular fibrillation thresholds of dogs subjected to repeat determinations on the same day and 1 day after initial determinations. Solid lines represent repeat thresholds on same day. Broken lines represent further determinations on same dog 1 day later.

periments for arterial hydrogen ion concentration, hemoglobin, arterial blood oxygen content, carbon dioxide content, and serum potassium. An attempt was made to return many of the animals to normal temperature and obtain survival.

The determination of ventricular fibrillation thresholds by the method outlined was made on the following groups of animals: (1) normothermia—93 dogs; (2) normothermia with temporary occlusion of the anterior descending ramus of the left coronary artery—21 dogs; (This was accomplished by occluding the left anterior descending coronary artery distal to its junction with the circumflex between a finger anteriorly and a Lahey forceps placed behind the artery for periods not exceeding 3 minutes. Stimulation was not started until 1 minute had elapsed from the time of occlusion to allow definite ischemia to develop.) (3) normothermia—repeat tests on the same day or upon subsequent days—10 dogs; (4) hypothermia from 37 to 20 degrees C.—12 dogs; (5) hyperthermia from 37 to 40 degrees C.—8 dogs; (6) hyperthermia with temporary occlusion of the anterior descending ramus of the left coronary artery—8 dogs; and (7) monkeys at normothermia, hyperthermia, and hypothermia—2.

RESULTS

Normothermic dogs—93. Initially, control studies were done on 93 dogs at 37 to 38 degrees C. to establish the normal range of ventricular fibrillation threshold. An average fibrillation threshold of 20.8 milliamperes was found with a range from 11.0 to 32.5 milliamperes.

Normothermic dogs with coronary occlusion—21 dogs. The fibrillation threshold in the area of ischemia fell from an average of 20.8 milliamperes before occlusion to an average of 4.9 milliamperes following occlusion. This level is extremely dangerous and close to the level at which spontaneous fibrillation will occur. The range was from 1 to 10 milliamperes. Similar results have been reported by Wiggers (7) and by Shumway, Johnson, and Stish.

Normothermic dogs—repeat tests—10 dogs. The influence of repeat fibrillation and de-

TABLE I.—PHYSIOLOGIC DATA ON NORMOTHERMIC AND HYPOTHERMIC DOGS

	Normothermia						*Hypothermia*						
Dog No.	*Pulse*	*Mean B.P.*	*pH*	*Vol. per cent CO_2*	*Per cent sat. O_2*	*Threshold in ma.*	*Pulse*	*Mean B.P.*	*pH*	*Vol. per cent CO_2*	*Per cent sat. O_2*	*Temp., °C.*	*Threshold in ma.*
1734	120	150	7.55	34.94	98.0	22.5	100	130	7.45	36.18	92.0	33.2	17.0
1739	150	110	7.64	30.23	95.0	20.0	60	60	7.71	21.43	91.0	27.5	16.0
1753	160	135	7.57	32.18	95.0	22.5	40	70	7.80	20.92	96.0	25.0	12.5
							20	40	7.85	12.77	95.0	20.5	9.5
1761	160	100	7.40	39.4	89.0	22.0	120	100	7.62	33.75	92.0	29.6	9.5
							50	85	7.70	29.73	94.0	23.8	4.0
1793	160	130	7.62	31.32	—	32.0	120	130	7.69	29.08	100.0	31.0	16.0
							80	100	—	20.06	97.0	26.8	11.0
							40	70	7.9	18.34	98.0	24.0	6.0
1802	150	—	7.79	28.94	98.0	20.0	95	—	—	22.81	97.0	29.9	15.0

fibrillation upon the threshold was determined. Fibrillation and prompt defibrillation up to 6 times in 1 day over a period of 7 hours did not change appreciably the threshold in the individual dog. The results of this study are illustrated in Figure 1 and show a maximum range of 2.5 milliamperes between any two tests on the same dog. Damaged hearts that were not promptly defibrillated showed a decrease in the threshold. Repeat tests of ventricular fibrillation threshold on subsequent days showed no significant difference. Although there is a wide variation in ventricular fibrillation threshold from animal to animal, the individual animal maintains a remarkably constant threshold on repeat tests.

Hypothermia—12 dogs. The alteration in ventricular fibrillation threshold, pulse, blood pressure, hydrogen ion concentration, carbon dioxide content, and arterial oxygen saturation induced by hypothermia is illustrated in Table I and Figure 2. No difference was noted between dogs cooled rapidly in an ice bath and those cooled slowly using a Therm-O-Rite apparatus. There is a progressive decrease in ventricular fibrillation threshold as the temperature of the animal is lowered. This begins immediately on cooling. The difference in threshold between the animals at normothermia and hypothermia could not be attributed to differences in arterial oxygen saturation, hydrogen ion concentration, or carbon dioxide content.

Hyperthermia—8 dogs. The influence of hyperthermia upon ventricular fibrillation thresholds, pulse rate, blood pressure, hydrogen ion concentration, arterial oxygen content, carbon dioxide content, and potassium is illustrated in Table II and Figure 3. There is a marked increase in the threshold in dogs heated to 40 degrees C. (104 degrees F.). Furthermore, survival after severe cardiac damage greatly exceeds that seen after hypothermia. Hyperthermic dogs often defibrillate spontaneously and are defibrillated with greater ease when this state exists than in normothermic or hypothermic animals. The difference in ventricular fibrillation threshold between the animals at normothermic levels and hyperthermic levels could not be attributed to differences in arterial blood oxygen saturation, hydrogen ion concentration, carbon dioxide content, or to serum potassium concentration.

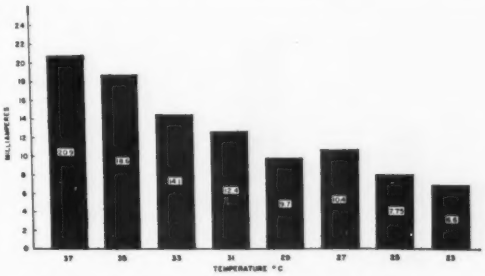

FIG. 2. Average ventricular fibrillation threshold in milliamperes of 12 dogs undergoing hypothermia.

Hyperthermia with coronary occlusion—8 dogs. Occlusion of the anterior descending ramus of the left coronary artery lowers the ventricular fibrillation threshold in hyperthermic animals but the level still remains above that found in normothermic dogs without coronary occlusion (Fig. 3).

Results in 2 monkeys. Figure 4 shows the fibrillation threshold in milliamperes during hyperthermia and hypothermia. Table II shows the pulse, blood pressure, hydrogen ion concentration, carbon dioxide content, arterial oxygen saturation, and serum potassium concentration of the two monkeys subjected to hyperthermia. The monkeys showed an even greater elevation of fibrillation threshold during hyperthermia with decline to dangerous levels on cooling.

DISCUSSION

The ventricular fibrillation threshold is best determined by stimulating the heart directly with a single square wave, electrical stimulus of known strength, known duration, at a known measurable and alterable time in the cardiac cycle. The quantitative results obtained by this technique are reproducible and readily applicable to the study of chemical, physical, and physiologic fac-

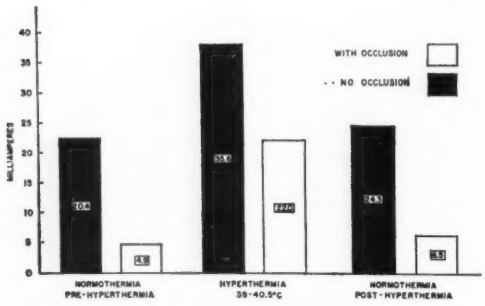

FIG. 3. Average ventricular fibrillation threshold in milliamperes of 8 dogs undergoing hyperthermia with and without left anterior descending coronary artery occlusion.

tors which influence the resistance of the heart against or propensity to ventricular fibrillation. Since ventricular fibrillation is a frequent consequence of coronary occlusion we believe this quantitative technique to be superior to determining how many animals with or without a cardiac revascularization operation succumb following coronary occlusion.

The present investigation confirms the widely held opinion that hypothermia predisposes the heart to ventricular fibrillation. We did not expect the rapid decline in threshold from 37 degrees C. but expected a relatively normal threshold to approximately 30 degrees C. It is quite possible during operation upon infants and children for their temperature to drop to 32 degrees C. We have recently begun monitoring rectal temperature in infants, children, and in seriously ill patients in whom factors other than lowered temperature might predispose to ventricular fibrillation. A Therm-O-Rite machine blanket on the operating table is then used to correct the hypothermia during the operative procedure. Lillehei on the basis of clinical experience has been using this technique for some time. These findings could also have some influence on the use of hypothermia or perfusion of cold blood as an adjunct to open heart surgery. Certainly complete and rapid return of the patient to normothermia after the use of this technique would appear to be indicated.

The markedly elevated ventricular fibrillation threshold found in all hyperthermic animals may also have some clinical application especially since coronary occlusion does not lower the threshold below that found at normothermia without coronary occlusion. There may be an advantage in treating certain patients with acute coronary occlusion and myocardial infarction with induced hyperthermia. Woods and Barnes have noted that, among patients with 1 or more premature ventricular beats in every 10 normal beats, 14 of 17 died of ventricular fibrillation, whereas all of a control group with 1 premature beat in 20

TABLE II.—PHYSIOLOGIC DATA ON DOGS AND MONKEYS WHILE NORMOTHERMIC AND HYPERTHERMIC

	Normothermia							*Hyperthermia*						
Dog No.	*Pulse*	*Mean B.P.*	*pH*	*Vol. per cent CO_2*	*Per cent sat. O_2*	*K mEq./l.*	*Threshold in ma.*	*Pulse*	*Mean B.P.*	*pH*	*Vol. per cent CO_2*	*Per cent sat. O_2*	*K mEq./l.*	*Threshold in ma.*
1820	160	—	7.77	22.96	99.0	3.3	32.0	200	—	7.65	30.66	94.0	3.4	46.0 47.0
1824	150	—	7.67	29.87	96.0	3.7	17.5	180	—	7.64	26.33	95.0	4.4	41.0
1828	160	110	7.71	29.54	96.0	3.9	17.5	140	110	7.70	27.62	86.0	3.7	25.0
1829	180	110	7.56	22.84	98.0	2.8	23.0	180	138	7.60	23.10	94.0	3.5	32.0
1831	120	110	7.66	27.84	95.0	3.5	17.0	140	115	7.47	32.58	99.0	4.3	31.0
1833	160	120	7.56	38.24	92.0	3.6	19.0	200	130	7.35	24.84	97.0	5.4	32.5
1865	200	120	7.36*	48.84*	85.0*	3.8	20.0	180	120	7.61	25.34	91.0	—	38.0
Monkey No.														
1	160	45	7.73	33.0	99.2	3.9	21.0	200	60	7.69	43.59	91.0	3.3	49.0
2	180	35	7.41	25.72	90.0	5.6	8.0	260	90	7.32	37.59	85.0	5.7	45.0

*Before thoracotomy.

or more survived. Patients likely to develop ventricular fibrillation after coronary occlusion selected on a basis such as this may respond well to induced hyperthermia for 48 to 72 hours. Likewise patients who are poor risks for operations designed to increase the blood supply to the heart or to increase intercoronary anastomoses might become better risks under hyperthermia. One would be dissuaded from using this technique clinically without first knowing other, perhaps undesirable, effects of hyperthermia on the cardiovascular system.

The circulatory responses to hyperthermia have been carefully studied by Prec and co-workers. These investigators found an increase in pulse rate of 39 beats per minute after heating dogs to 42 degrees C. There was no change in cardiac output with heating from 33 degrees to 40 degrees C. There was no consistent change in blood pressure or arterial oxygen content. There was a slight decrease in arterial carbon dioxide content. No measurable change in cardiac efficiency was noted.

Maxwell and co-workers have also studied this problem in dogs heated to an average of 106 degrees F. In contrast to Prec's investigation these workers found an increase in cardiac output and slight decrease in myocardial efficiency. A greater increase in pulse rate at the higher average temperature used in this study may account for this adverse effect. Hyperthermia did decrease coronary resistance and thereby increased coronary blood flow.

The ease with which hyperthermic hearts are defibrillated and the higher incidence of long term survival in these animals in the present study suggest that hyperthermia as here utilized has no outstanding adverse effect on the organism.

The precise mechanism for difference in threshold between cold and warm hearts is not readily apparent. There is no evidence for oxygen lack in either state. The increased incidence of ventricular fibrillation in hypothermia has been attributed to the development of heterogenicity among individual muscle fibers in that state. There is an irregularity of response due to different speeds of conduction and refractoriness in many of the active fibers. The heterogenicity of active cardiac muscle fibers predisposes to ventricular fibrillation. It is postulated that heterogenicity predominates in hypothermia, is less at normothermia, and still less in the hyperthermic heart.

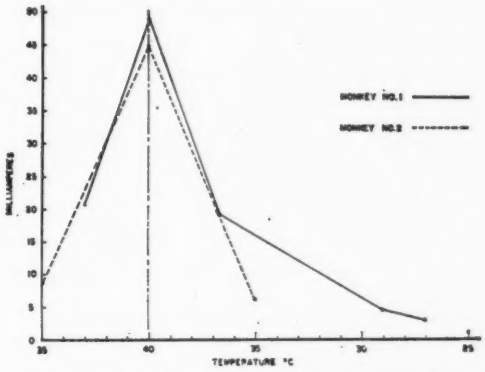

FIG. 4. Alterations in ventricular fibrillation thresholds of 2 monkeys with changes in cardiac temperature.

The question might be raised as to whether the stimuli actually reach the muscle fibers during the vulnerable period when there is a marked change in pulse rate, conduction time, and refractoriness of the heart due to alteration in temperature. However, it must be noted that with a stimulus of 10 milliseconds' duration, each succeeding stimulus is delivered with a delay period from the R wave which progressively increases by 5 milliseconds. Therefore, there is actually an overlap of stimulation to the various segments of the cardiac cycle regardless of heart rate, conduction time, or refractory period, though the individual cycles receive only 1 stimulus.

One of the most interesting findings of this study concerns investigations of ventricular fibrillation. It is known that the temperature of many animals drifts downward during a long procedure while under anesthesia or can be elevated as a result of an infection. Monitoring the temperature or, even more important, maintaining it at

normothermia in such studies would appear to be mandatory.

In establishing and maintaining cardiac action following cardiac arrest or ventricular fibrillation, attention should be directed to keeping body temperature at or above normal.

We have become more cognizant of the possible dangers of rapid infusions of cold blood since obtaining the data here reported.

SUMMARY AND CONCLUSIONS

Ventricular fibrillation thresholds have been determined in the dog and monkey in the normothermic, hypothermic, and hyperthermic states. This has been done by utilizing electronic equipment which provides a single square wave electrical stimulus of known strength, known duration, which is delivered directly to the heart at a known, measurable and alterable time in the cardiac cycle.

The fibrillation threshold for a given animal is remarkably constant even after repeat tests on the same day or upon retesting on subsequent days.

Coronary occlusion causes a marked decline in threshold in the area of the infarct.

There is a marked elevation of the fibrillation threshold in dogs and monkeys which are hyperthermic (40 degrees C.). Coronary occlusion in the hyperthermic animal causes a decline in the fibrillation threshold but this still remains at or above the level seen in normothermic animals without coronary occlusion.

Hypothermia causes a progressive decline in fibrillation threshold. The rapidity of cooling does not appear to influence this.

The importance of measuring the temperature or, more important, maintaining it at normothermia in experimental studies of ventricular fibrillation is stressed.

The possible mechanism responsible for the alteration in threshold and the clinical applications are discussed.

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ACTIVE IMMUNIZATION AGAINST TETANUS WITH INTRADERMAL TOXOID

OSCAR P. HAMPTON, JR., M.D., F.A.C.S., St. Louis, Missouri and
JOHN HARD, M.D., Metropolis, Illinois

DATA have been obtained by using intradermal tetanus toxoid in humans to produce an active immunization against tetanus. The project was initiated to determine whether alum-precipitated tetanus toxoid could be given intradermally without skin slough and how rapidly a protective level of antitoxin in the serum (an active immunity) could be obtained with intradermal tetanus toxoid repeated at short intervals.

Aluminum phosphate-adsorbed tetanus toxoid in doses of .5 cubic centimeter was given intradermally at intervals of 3 days, that is, on the first, fourth, and seventh days. Each .5 cubic centimeter was actually divided into 3 portions of approximately .15 to .2 cubic centimeter and given in 3 different areas within a radius of 1 inch on the anterior thigh. The subjects were 10 adult volunteers who, to their knowledge, had never previously received either active or passive immunization against tetanus.

Blood samples were drawn for mouse titration of the antitoxin titer: (1) just prior to the first injection of intradermal tetanus toxoid on the first day to verify that the subjects were not already carrying a high titer, (2) just prior to the third injection on the seventh day, (3) on the fourteenth day, and finally (4) on the twenty-seventh day after first injection. Results are shown in Table I.

Only a mild and definitely tolerable amount of discomfort was experienced during the intradermal injections. No skin sloughs were obtained. Local reactions were practically nil with the first injections. With several of the second and third injections, small hard nodules formed and persisted in the skin, and, in a few instances, a small area of the outer skin peeled away as in a very superficial second degree burn and oozed a small amount of serum. These healed rapidly under mere band-aid protection.

From Department of Surgery, St. Luke's Hospital, St. Louis.

Analysis of the data shown in Table I demonstrates that on the seventh day only a trace of antitoxin was present in only half the subjects. On the fourteenth day all subjects showed a serum titer which at least was only slightly less than .01 unit per cubic centimeter. By the twenty-seventh day all subjects had a titer of .01 or as a rule greater than .01 unit per cubic centimeter. Several had between .01 and .1 and 1 had 8 units per cubic centimeter. Perhaps the data on this subject should be discarded since the first specimen actually showed a trace of antitoxin, and the rapid rise in titer thereafter suggests that this patient had been actively immunized against tetanus previously.

APPRAISAL OF RESULTS

A concentration of .01 unit of antitoxin per cubic centimeter has been generally accepted as the level required to protect a human from tetanus. By this standard, it has been demonstrated that a protective level of antitoxin can be obtained by at the most the twenty-seventh day with intradermal injections of aluminum phosphate-adsorbed tetanus toxoid in a dosage of .5 cubic centimeter repeated at intervals of 3 days until 3 injections have been given.

Of greater significance, perhaps a protective level was established sooner in these volunteers, probably by the fourteenth day and even possibly by the eighth or ninth day. Varney states that .001 unit of actively produced antitoxin per cubic centimeter of serum will protect a mouse against a huge

TABLE I.—TETANUS ANTITOXIN TITERS IN SERA FROM VOLUNTEERS AFTER INTRADERMAL TETANUS TOXOID

Volunteer No.	*Specimen A—1st day Titer, units/ml.*	*Specimen B—7th day Titer, units/ml.*	*Specimen C—14th day Titer, units/ml.*	*Specimen D—27th day Titer, units/ml.*
1	*	*	<1/100	possibly 1/100
2	*	*	<1/100‡	1/100
3	*	*	<1/100	1/10
4	trace	trace?	possibly 1/100	1/100+, 1/10−
5	trace	>1/10	>1‡	8 ±
6	*	trace?	1/100+, 1/10−	1/100+, 1/10−
7	*	trace?	<1/100	†1/100+, 1/10−
8	*	trace?	<1/100	1/100+, 1/10−
9	*	*	possibly 1/100	*Vial broken*
10	*	trace?	<1/100	1/10+, 1−

*0.5 ml. showed no protection versus 1 mouse MLD of toxin.
†On the 27th day this subject showed only a trace but a repeat specimen gave the results shown in the table.
‡Taken on 20th day.

injection of toxin, and he and others are of the opinion that this concentration in the human is protective particularly because the concentration of antitoxin is on the uptrend if a booster injection of toxoid has been given or if tetanus toxin is being produced within the tissues. This reasoning is supported by the fact that the mere inoculation of tetanus bacilli or spores into an area of dead or devitalized tissue in an animal or human with some previously established active immunity will cause an increase in titer. In addition, an actively produced immunity is of a much greater protection than a passively produced immunity. D. d'Antona and M. Valmesin in 1937 demonstrated that .012 to .05 unit of antitoxin per cubic centimeter produced actively in guinea pigs protected against 200 minimum lethal doses of toxin whereas 5 to 10 times more antitoxin given passively failed to withstand the 200 minimum lethal doses of toxin. Unfortunately in the studies here reported, the antitoxin in the serum was not titrated to show amounts significantly lower than .01 unit per cubic centimeter. It is possible that on the seventh day after the first injection those volunteers showing a trace of antitoxin actually had .001 unit per cubic centimeter and may have already established a protective level.

CONCLUSIONS

1. Aluminum phosphate-adsorbed tetanus toxoid may be given intradermally in .15 to .2 cubic centimeter doses without resulting slough of the skin. An occasional superficial ulcer which heals quickly may be seen. Small nodules at site of injection may persist several weeks. Injections produce only a tolerable discomfort for a period of a few moments.

2. In humans, .5 cubic centimeter of such toxoid injected intradermally on the first, fourth, and seventh days will produce a measurable amount but somewhat less than .01 unit of tetanus antitoxin per cubic centimeter of blood by the fourteenth day.

3. On or before the twenty-seventh day this concentration of actively produced antitoxin will reach .01 to 1, and sometimes more, unit per cubic centimeter of blood.

4. If .001 unit of actively produced antitoxin which is steadily increasing in concentration protects against tetanus, probably an active immunity can be produced in 7 to 10 days with intradermal aluminum phosphate-adsorbed tetanus toxoid.

5. Further study on these problems is indicated, particularly, to determine in animals if .001 unit of actively produced antitoxin per cubic centimeter which is on the uptrend will protect against a heavy inoculation of tetanus spores under conditions favoring the development of tetanus.

6. If .001 unit per cubic centimeter will protect in animals, this study should be repeated in order to show how quickly this concentration can be produced in the human being.

PREOPERATIVE ROENTGEN THERAPY FOR CANCER OF THE RECTUM

M. W. STEARNS, JR., M.D., F.A.C.S., MICHAEL R. DEDDISH, M.D., F.A.C.S., and STUART H. Q. QUAN, M.D., F.A.C.S., New York, New York

THE USE of radiation therapy as an adjunct to surgical resection for cancer of the breast and cervix is a much discussed subject; but there are relatively few published data—practically none in the English language—concerning its use as an adjunct to the surgical management of rectal cancer. Because irradiation of one kind or another has been used in the treatment of cancer of the rectum at Memorial Center for many years, a review of this experience has been undertaken to determine whether or not there is any indication that radiation therapy has a significant role in the treatment of rectal cancer.

From the late 1920's through the 1930's considerable effort was made to treat carcinoma of the rectum solely by various methods of ionizing radiation. Interstitial radium and radon, radium applicators and packs, and high voltage roentgen rays were used extensively enough to prove that, except in a small number of patients, these modalities could not be considered curative for these lesions. By the end of the 1930's these agents were no longer used for patients considered amenable to cure. However, it was concluded that roentgen therapy was the most generally useful agent in the palliative management of patients with large bowel primary cancer who had inoperable, recurrent, or metastatic carcinoma. Moreover, cycles of high voltage (200 to 250 kv.) roentgen rays to the pelvis were given prior to surgery to many patients with rectal cancer through the 1940's. This review pertains to the experience acquired with preoperative x-ray therapy during these years.

From the Rectum and Colon Service, Memorial Center for Cancer and Allied Diseases, New York.

MATERIAL AND DATA

To evaluate possible effects of preoperative x-ray therapy in the management of patients with cancer of the rectum, we have reviewed the charts of all patients with histologically proved adenocarcinoma of the rectum or rectosigmoid not previously subjected to surgery who were seen by members of the Rectal and Colonic Service of Memorial Center during the years 1939 to 1951, a total of 1,786 patients. Five hundred and ten of these were not subjected to celiotomy. These included patients who were seen in consultation only, those who refused proffered treatment or failed to complete treatment started, as well as those considered inoperable.

The over-all operability rate was 72 per cent. Of the 1,276 who submitted to exploratory procedures, 971 (77 per cent) had resections of the involved segment of bowel, an over-all resectability rate of 52 per cent.

The entire group subjected to celiotomy was divided into: (1) those who did not receive preoperative roentgen therapy, and (2) those who did. The preoperative cycle was given with a 250 kilovolt unit (rarely a 200 kv. unit) with 1.5 millimeter copper filter. Usually 6 (occasionally 4) pelvic fields, roughly 11 by 14 centimeters, were used; and, if the primary tumor was located within 8 centimeters of the anal verge, a 10 centimeter circular perineal field was added. The beam was directed at the primary tumor with the center of the field at the level of the tumor; the target skin distance was 70 centimeters for the pelvic portals and 50 centimeters for the perineal portal. Each field received 450 roentgens in air per ex-

TABLE I.—OPERATIVE MORTALITY

	Total patients	*Postoperative deaths*	*Operative mortality, per cent*
Operated upon	1276	37	2.8
No x-ray	549	14	2.6
With x-ray	727	23	3.0
Resected	971	22	2.3
No x-ray	473	11	2.3
With x-ray	498	11	2.2

TABLE II.—FIVE YEAR SURVIVAL

	Total patients	*Five year survivors*	*Five year survival rate, per cent*
Total series	1786	505	28.5
Operated upon	1276	479	37.4
No x-ray	549	225	41.0
With x-ray	727	254	35.0
Resected	971	479	49.0
No x-ray	473	225	47.5
With x-ray	498	254	51.0

posure. The 2 anterior fields were each treated once, while the posterior and posterolateral portals were each treated twice. The average tumor dose was calculated to be not over 2,000 roentgens. There were 549 who had not had preoperative irradiation and 727 who had. Of the group subjected to celiotomy, 971 had resections. Of those resected, 473 had not had preoperative x-ray therapy and 498 had. The resectability rate, then, among those subjected to celiotomy who had not had preoperative x-ray therapy was 86 per cent; it was 69 per cent for those who had.

The operative mortality is presented in Table I. The over-all mortality was 2.8 per cent, while the operative mortality for those subjected to resection was 2.3 per cent. There was no difference between those having had previous roentgen therapy and those who had not.

The data related to survival are incorporated in Table II. There were 505 patients who survived 5 or more years, an over-all survival rate of 28.5 per cent. The 5 year survival rate of those subjected to operation was 37.4 per cent, and in those having some type of resection, 49 per cent. It should be emphasized that these are over-all figures; cases considered as failures were those patients who were lost to follow-up or who died of other causes, without evidence of cancer, in less than 5 years, as well as those who had distant metastasis when treated.

The patients operated upon were divided into groups on the basis of preoperative irradiation. The over-all 5 year survival rate was 41 per cent for those who did not receive treatment preoperatively and 35 per cent for those who did. When the patients having resection of the primary neoplasm were similarly grouped, the 5 year survival rate in those not having preliminary x-ray therapy was 47.5 per cent against 51 per cent for those who did. This figure includes those having palliative resection in the presence of distant metastasis.

In an effort to determine whether preoperative roentgen therapy might be of value in particular types of patients or tumors, the patients having resections were separated on the basis of age, sex, grade of tumor, and the Dukes classification of the resected specimen. These data are contained in Tables III to VI. It may be seen that preoperative x-ray therapy apparently influenced survival favorably only in those patients with lymph node metastasis in the resected specimen. The survival rate in those without x-ray treatment was 23 per cent; in those who had received such treatment, 37 per cent.

Table VI also indicates that the relative distribution of Dukes' A, B, and C lesions was similar in both series. The indetermin-

TABLE III.—SURVIVAL AND AGE

Age, years	*No. of patients*	*Five year survival rate, per cent*
Under 40		
No x-ray	28	43
With x-ray	36	70
40 to 49		
No x-ray	75	62
With x-ray	99	55
50 to 59		
No x-ray	133	52
With x-ray	152	48
60 to 69		
No x-ray	138	49
With x-ray	151	53
Over 70		
No x-ray	42	33
With x-ray	38	37

ates include those who died postoperatively and those who died of other causes without evidence of recurrent or metastatic cancer in less than 5 years, as well as those who were lost to follow-up. The determinate 5 year survival figures exclude those operated upon for palliation, and the indeterminate patients.

The incidence of gross metastasis to the liver as related to preoperative x-ray therapy is reviewed in Table VII. The over-all incidence in those with and without preoperative irradiation was 18.5 per cent and 11.2 per cent, respectively. An effort was made to ascertain whether this higher incidence of gross liver metastasis was a reflection of undue delay introduced by administration of preoperative irradiation. Thus, the patients were grouped and compared according to equal time intervals which elapsed between the dates of initial x-ray therapy and surgery for those who received preoperative irradiation, and between the dates of initial visit and surgery for those who had not had such x-ray therapy.

TABLE IV.—SURVIVAL AND SEX

	No. of patients	*Five year survival rate, per cent*
Males		
No x-ray	302	48
With x-ray	380	40
Females		
No x-ray	169	53
With x-ray	188	56

TABLE V.—SURVIVAL AND GRADE OF TUMOR

Grade tumor	*No. of patients*	*Five year survival rate, per cent*
I		
No x-ray	7	73
With x-ray	8	75
II		
No x-ray	232	57
With x-ray	238	61
III		
No x-ray	101	43
With x-ray	178	47
IV		
No x-ray	6	17
With x-ray	6	33

DISCUSSION

The first striking difference shown in this review is in the resectability rates between those who did not have preoperative irradiation (86 per cent) and those who did (69 per cent). That is, the patients who had received preoperative x-ray appeared to have a significantly lower resectability rate. In evaluating the significance of this disparity, one must consider the fact that all patients seen, regardless of the state of operability, are included. All patients considered borderline operable received x-ray therapy before exploration. This group also includes a large number of patients who were deemed inoperable and treated by irradiation. Subsequently, a colostomy was performed merely to relieve obstruction. Because of these considerations, we believe that the lower resectability rate in the patients with preoperative irradiation cannot be ascribed solely to the use of this preliminary treatment.

Under these conditions, it is our opinion that it is more meaningful to determine dif-

TABLE VI.—SURVIVAL AND DUKES' CLASSIFICATION

Dukes' classification	*No. of patients*	*Incidence in series, per cent*	*Liver metastasis*	*Indeterminate*	*5 year survivors*	*Over-all 5 year survival, per cent*	*Determinate 5 year survival, per cent*
A							
No x-ray	96	21	0	8	69	72	79
With x-ray	103	23	2	15	75	73	85
B							
No. x-ray	145	33	0	12	92	63	70
With x-ray	161	35	2	12	104	64	72
C							
No x-ray	201	46	19	10	46	23	27
With x-ray	195	43	13	14	72	37	43

TABLE VII.—LIVER METASTASIS

	No. explored	*Metastasis present*	*Incidence of metastasis, per cent*
No x-ray	540	62	11.2
With x-ray	757	138	18.5
Time interval to surgery			
Under 1 month			
No x-ray	476	57	12
With x-ray	184	25	14
1 to 3 months			
No x-ray	42	4	10
With x-ray	466	89	19
3 to 6 months			
No x-ray	11	1	10
With x-ray	72	19	27
Over 6 months			
No x-ray	13	2	15
With x-ray	39	18	46

ference in survival attributable to x-ray therapy by comparing patients who had resections, instead of all patients operated upon. Thus, the study of the over-all survival rate in the entire operative group indicated a survival rate of 41 per cent for those who did not have preoperative irradiation against 35 per cent for those who did. The resected group revealed a survival rate of 47 per cent for those who had not had x-ray against 51 per cent for those who had. These figures would appear to indicate that the chance of long survival was not adversely affected by preoperative irradiation.

That preoperative irradiation actually benefited certain patients is indicated in Table VI in which the series is studied according to Dukes' classification. This shows that, although preoperative x-ray therapy did not influence the survival rates in patients without lymph node metastasis, it did improve the survival in those with lymph node metastasis from 23 per cent to 37 per cent. This improved over-all survival rate of 14 per cent in a series of this size is a highly significant figure. Thus, even though preoperative x-ray therapy had no appreciable effect on lesions treated satisfactorily by standard surgical methods, it did substantially improve the salvage in the group currently having the poorest surgical outlook.

Another interesting finding in this review was the significantly higher incidence of liver metastasis in patients with preoperative x-ray therapy—18.5 per cent compared with 11.2 per cent in those without. The explanation for this may lie, at least in part, in the fact that all those patients considered inoperable or borderline operable had preoperative x-ray therapy. That this may not be the entire explanation is implied in the fact indicated in Table VI, namely, that with longer time intervals before surgery, the incidence of liver metastasis appears to increase more rapidly among those treated with x-ray. Differences are statistically significant when the delay was over 6 months. This observation, taken in conjunction with the apparent progressive increase over the shorter intervals, suggests that preoperative x-ray therapy to a rectal cancer may give rise to a greater incidence of liver metastasis when delay occurs before surgery is performed. From the data available it would seem that, if surgery is performed within a reasonable time (1 month) after x-ray therapy has been given, no increased risk of liver metastasis exists. However, it can be argued that this is an evaluation only of gross liver metastasis palpable at the time of operation.

If there were some way of determining preoperatively the presence of lymph node metastasis, the decision when to employ preoperative irradiation would be simple. However, since this cannot be determined, the decision is more difficult. Although these data do not provide unequivocal evidence for or against preoperative irradiation in cancer of the rectum, some of the observations should be emphasized. For example, even though the survival rates are not significantly higher in the resected group with preoperative x-ray, poorer results cannot be attributed to the use of preoperative irradiation per se. The fact demanding the most serious consideration is that preoperative x-ray therapy did improve substantially the survival rate in patients in need of most help—those with lymph node metastasis.

There are several opposing considera-

tions: (1) The delay introduced by x-ray therapy, while not affecting patients' survivals, can cause serious mental disturbance to the patient who knows he has a malignant tumor requiring surgery. (2) The course of x-ray therapy introduces an additional financial burden of not inconsiderable expense. (3) A frequently expressed objection to preoperative irradiation is that it makes surgery more hazardous. This does not seem to be borne out by our experience, since the operative mortality rates are the same. At worst, some increased vascularity results, and perhaps some delay in wound healing.

It is our considered opinion that, until better criteria have been established for selecting patients for preoperative irradiation (or an equally effective adjunct to surgery is developed) patients with adenocarcinomas of the rectum should undergo prescribed cycles of x-ray therapy. This opinion is based on the improved survival rate in patients currently having the poorest prognosis, those with metastasis to mesenteric lymph nodes.

SUMMARY

1. Statistics on 1,786 patients with primary adenocarcinoma of the rectum or rectosigmoid seen at Memorial Center between 1939 and 1951 are reviewed.

2. Of these patients 1,276 were subjected to celiotomy and, for purposes of this study, have been separated into: those receiving preoperative x-ray therapy—727; and those not receiving such treatment—549.

3. In the first group the resectability rate was 69 per cent, compared with 86 per cent in the second group. Probable explanations for this difference are given.

4. The over-all 5 year survival rate in the entire series was 28.5 per cent. The survival rate in those subjected to celiotomy was 37.4 per cent; it was 49 per cent in those in whom a resection was performed.

5. In those patients subjected to celiotomy, when preoperative irradiation had not been given, the 5 year survival rate was 41 per cent; it was 35 per cent with therapy.

6. When resection was accomplished, the 5 year survival rate was 47.5 per cent if no irradiation had been given preoperatively, and 51 per cent if it had.

7. Age, sex, and grade of tumor did not appear to bear any relation to possible selection of patients for preoperative x-ray therapy.

8. Preoperative x-ray therapy did not appear to influence the survival rate in patients free of lymph node metastasis but definitely benefited those demonstrating lymphatic spread. Thus, in the group with metastasis, there was a 23 per cent 5 year survival rate in those not subjected to preoperative irradiation and 37 per cent in those who were.

9. In this series the incidence of liver metastasis was significantly higher in those who had preoperative irradiation than in those who had not. The probable explanation for this is given. Furthermore, as the time lag between initial visit or administration of x-ray therapy and surgery increased, the incidence of liver metastasis remained rather constant in the group that had not had preoperative x-ray therapy, but increased quite rapidly among those who had.

10. On the basis of the findings of this study, we have resumed the use of preoperative irradiation in patients with adenocarcinomas of the rectum.

ESOPHAGEAL HIATAL HERNIA

L. C. SMITH, M.D., and H. H. BRADSHAW, M.D., F.A.C.S., Winston-Salem, North Carolina

SYMPTOMATIC esophageal hiatal hernias present a major problem in management to the internist and surgeon. The many methods of management described in the literature support the fact that no one method is best suited for all cases. This article is presented to review briefly the subject of esophageal hiatal hernia, give some ideas about certain points in management, and to review the cases in which operation was performed at the North Carolina Baptist Hospital.

INCIDENCE

In from 2 to 9 per cent of upper gastrointestinal cases an esophageal hiatal hernia is demonstrated. This incidence is second only to duodenal ulcer in frequency. It is more common in middle age but may be found in very young and old. Many esophageal hiatal hernias are symptomatic and require treatment.

CLASSIFICATION

There are two main types of esophageal hiatal hernias, the sliding and the paraesophageal. These usually occur separately but occasionally they may occur together. Previously, a congenitally short esophagus was thought to be a contributing factor, but the increasing employment of transthoracic hernioplasty has shown it to be relatively uncommon. Even though the esophagus appears shortened by x-ray and esophagoscopic examinations, it can be freed and stretched to its normal length with ease in the presence of an uncomplicated hernia. In a recent review of the literature, the incidence of congenitally short esophagus was found to vary from 0.5 to 5 per cent in sliding hiatal hernias. There was no true congenitally short esophagus in this series of 73 cases of primary repair of the hernia.

From the Department of Surgery, Bowman Gray School of Medicine and North Carolina Baptist Hospital, Winston-Salem, North Carolina.

SYMPTOMS

Symptoms produced by the sliding type of hiatal hernia are essentially those due to reflux esophagitis and its complications. These are usually "heartburn," acid eructation, substernal pain or fullness, dysphagia, and sometimes hematemesis. The symptoms are exaggerated usually in patients in the supine position or on bending over. Sometimes because of delay in proper diagnosis and inability of the patient to obtain relief, serious psychogenic symptoms may develop which confuse the picture. The substernal pain and fullness may be relieved if the erect position is assumed. The dysphagia may be improved, often temporarily, by esophageal dilation but this does not help the esophagitis. Bland foods and alkalis may relieve the indigestion or heartburn.

Paraesophageal hernias may cause a substernal fullness after meals (particularly in the prone position), vague indigestion, vomiting, severe cramping or constant pain, hematemesis, or melena.

The symptoms of either type of hernia are often confused with heart disease, peptic ulcers of the duodenum or stomach, and biliary tract disease. When one or more of these are associated with hiatal hernia, it may be difficult to determine which is the major problem.

FACTORS CONTROLLING COMPETENCY OF CARDIA

From current available data, there appear to be at least three factors which play a role in the competency of the esophagogastric junction. First, the acute angle at which the esophagus joins the stomach aids in preventing reflux. Second, even though an anatomic

sphincter does not exist, there is good evidence that a physiologic sphincter does exist. In 1 of our patients there was a complete ring of hypertrophied circular muscle, 1 centimeter thick, involving the lower third of the esophagus. It resembled that seen in hypertrophic pyloric stenosis. Third, the manner in which the fibers from the right crus of the diaphragm completely encircle the esophageal hiatus is also thought to play an important role in preventing reflux into the esophagus.

DIAGNOSIS

The diagnosis is usually suspected from the history and is confirmed by x-ray studies or esophagoscopy. In many cases the diagnosis is missed because the history is not typical or because the symptoms are thought to be functional. The physician must suspect hiatal hernia and ask the radiologist to look for it. It is often necessary to do multiple roentgenologic examinations. Many patients with upper gastrointestinal bleeding from esophagitis with ulceration are thought to have a bleeding duodenal ulcer, and, indeed, both diseases may be present. The esophagoscopist can be of great help in looking for congenital rings, strictures, esophagitis with or without ulceration, and a double pinchcock which indicates a sliding type of hernia. In our experience, the esophagoscopist is of more aid in evaluating the sliding hernia, and the roentgenologist of more aid in diagnosing the paraesophageal type. Other causes for the symptoms should be eliminated.

COMPLICATIONS

The complications that occur secondary to sliding hiatal hernias are reflux esophagitis with ulceration, hemorrhage, and stricture. Massive hemorrhage occurs in about 10 per cent of patients with esophagitis. Simple repair of the hernia may provide adequate relief of symptoms except in those patients with dense fibrotic strictures. These may require more extensive surgery such as a Heller type of myotomy or resection of the involved esophagus. Those with minimal stricture do well with repair of the hernia and postoperative esophageal dilatations. Carver and Sealy reported 130 cases of esophagitis in which 76 per cent were due to hiatal hernia, 13 per cent followed surgical excision of the cardia and 11 per cent were apparently due to persistent vomiting.

The complications of paraesophageal hernia are incarceration, ulceration, hemorrhage, and occasionally strangulation with perforation.

TREATMENT

The treatment of choice is surgical repair of the hernia with restoration of the involved parts to as near normal as possible anatomically and physiologically, keeping in mind the three factors that aid in preventing reflux esophagitis. Medical management is effective in relieving some of the symptoms but it does nothing to correct the underlying abnormality. Such management is helpful in preparing the patient for surgery. Age alone should not be considered a contraindication to surgery. Many elderly people tolerate surgery very well. In this series of 73 patients who had primary repair of the hernia, there were 16 patients who were over 65 years of age and 7 of these patients were over 70 years of age. One patient was 84 years of age.

There is difference of opinion among surgeons as to whether the transthoracic or transabdominal approach is better. The transthoracic approach affords better exposure of the entire area involved. An adequate length of the lower esophagus can be freed from the surrounding structures with greater ease. This is very important in obtaining a successful repair of the hernia; the hernioplasty which creates tension on the esophagus will fail in many instances. The hernia sac is above the diaphragm and it can be dissected out with greater safety. If there are conditions present such as stricture, congenital rings, or penetrating ulcers, these can be handled better through the left side of the chest.

The transabdominal route affords the surgeon the opportunity to examine the abdominal viscera and to remove the gallbladder if it is diseased. Since 20 to 25 per cent of patients with nonfunctioning gallbladders are said to be asymptomatic, the occasional advantage afforded by the abdominal approach becomes obvious.

The most widely accepted method is the transthoracic repair of the hernia as described by Allison with minor variations depending on the surgeon. The chest is entered through the bed of the eighth or ninth rib. After dividing the inferior pulmonary ligament, the mediastinal pleura is incised vertically over the lower part of the esophagus with the incision being extended laterally over the aorta just above the diaphragm and medially toward the pericardium. The lower portion of the esophagus is freed and a tape placed about it. Care is taken not to injure the vagus nerve. The diaphragm is then incised for about 2½ inches radially, anterior to the spleen, with half the incision in the muscular portion and the other half in the tendinous portion. With the operator's finger placed through the opening in the diaphragm and into the hernia sac from below, the sac is opened ¾ inch from the esophagus in a circular manner. After the esophagus is completely freed from the diaphragm, the tape about the esophagus is passed through the hiatus, and the lower part of the esophagus and the stomach are pulled down below the diaphragm. Several interrupted silk sutures are used to suture the esophagophrenic ligament to the undersurface of the diaphragm. The cuff of hernia sac left on the esophagus makes the esophagophrenic ligament easy to identify. The crura are then sutured together with silk sutures posterior to the esophagus. The hiatus should admit the tip of the index finger along the side of the esophagus after the repair. The diaphragm is closed with interrupted silk sutures. The chest is drained with a thoracotomy tube connected to water sealed suction. The chest wound is closed in layers.

A point that should be stressed is that the patients with evidence of stricture or congenital ring associated with hiatal hernia should also have a gastrotomy. The surgeon should insert a finger into the lower part of the esophagus from the gastric side and examine for a stricture or a ring. If a stricture exists that cannot be dilated easily, a Heller type myotomy or a resection should be done depending on the severity of the stricture. If a mucosal ring is present, an esophagotomy should be done and the ring should be resected. If the ring is low enough in the esophagus it may be resected through the gastrotomy. In this series there were 4 patients with a mucosal ring. In 3 of these the condition was suspected preoperatively and treated properly. In 1, repair of the hernia had been carried out elsewhere with recurrence of symptoms and the hernia. The fourth was demonstrated by x-ray examination postoperatively because of persistent symptoms. It had been overlooked during repair of the hernia.

Some of the surgical procedures which have been advocated for the treatment of esophageal hiatal hernia with the complications listed earlier are as follows: left phrenic nerve crush; Finney pyloroplasty; subtotal gastric resection; vagotomy with pyloroplasty or gastrojejunostomy; Roux-Y esophagojejunostomy with exclusion of the stomach; interposition of a segment of jejunum or colon between the esophagus and stomach; and repair of the hernia. These are listed to emphasize inherent difficulties in treating the complications of esophageal hiatal hernia.

LOWER ESOPHAGEAL RINGS

Dysphagia is the most common symptom resulting from a lower esophageal ring. It is usually episodic and may be present for many years before causing severe difficulty. If a large bolus of solid food is swallowed, it may completely occlude the esophagus at the level of the ring. In 1 patient from our series obstruction was caused by a pill. In 1953, Schatski and Gray reported 5 cases of lower

esophageal rings. In 2 cases the symptoms could be reproduced by feeding the patients barium-filled gelatin capsules measuring 1 centimeter in diameter which were shown by x-ray examination to lodge at the level of the ring.

In the past, some investigators have believed that these rings were not fixed anatomic structures but rather folds of redundant mucosa. Recently, MacMahon, Schatski, and Gray reported in detail the pathologic findings in a patient with lower esophageal ring who died of an unrelated cause. There was a definite anatomic ring present. The superior surface was covered by esophageal mucosa and the inferior surface was covered with gastric mucosa. A circular bundle of smooth muscle was found near the free edge of the ring just beneath the mucosa and a thin layer of loose areolar tissue. We have had 2 patients with similar clinical and pathologic findings as proved by tissue removed at surgery.

Each of the 3 surgically repaired cases in our series was done by a different surgeon. All were repaired through the chest. In 1, a gastrotomy was done near the esophagogastric junction, and the ring could be felt with the examining finger (Fig. 1). It was about 3 centimeters above the cardia but could be moved in either direction for a distance to 6 to 7 centimeters. The lumen was about 7 millimeters in diameter. An esophagotomy was done and the ring was excised. The mucosal edges were approximated with a continuous suture of No. 000 chromic catgut. Pathologic sections of the tissue showed both surfaces to be covered with gastric mucosa. The other 2 cases were similar in that the rings were at the esophagogastric junction. They were definitely identified through a gastrotomy opening and repaired through it. The opening measured about 5 millimeters in diameter. One was repaired by making 2 vertical incisions in the ring and closing them horizontally. A wedge piece of the ring was removed for pathologic study. The superior surface of this ring was covered with esophageal mucosa. The third ring was corrected by making vertical incisions through it and oversewing the free edges of mucosa, without suturing them together, to control the oozing. An adequate lumen was maintained postoperatively by esophageal dilatations. A biopsy was not taken.

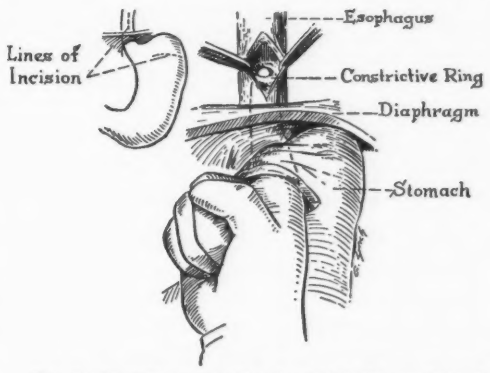

FIG. 1. Operative procedure by which the esophageal ring is located and palpated by the examining finger inserted through the gastrotomy wound.

ANALYSIS OF 84 CASES TREATED BY SURGERY

From 1944 through 1957, there were 84 cases of hiatal hernia treated surgically. There were 40 females and 44 males, a ratio of almost 1:1. In other series the ratio is as high as 4:1 female to male. In 11 of the 84 cases, only a left phrenic crush was performed. Phrenic crush does occasionally relieve symptoms of hiatal hernia, but it is a procedure which is rarely done at present. Five patients in this series obtained some relief. The remaining 73 patients underwent primary repair of the hernia. Fifty-eight had sliding hernias and 15 had paraesophageal hernias. In 6 of the 73 cases repair was done through the abdomen and in the remaining 67 through the left side of the chest. All those patients who had not been seen for follow-up examination in the previous 6 months were sent a questionnaire requesting information as follows:

1. Are you able to do your regular work?
2. Have you gained or lost weight?
   Gained_____pounds.
   Lost_____pounds.

3. Do you have difficulty in swallowing?
4. Do you have indigestion or heartburn?
   If yes, describe.
5. Do you consider the operation successful?
6. Do you consider yourself:
   Cured ————
   Improved———
   Not improved —
7. Give any additional information below.

Most of the patients responded promptly. In some instances information was obtained from the referring physician. All patients were observed for from 6 months to 13 years except 1 who has been lost to follow-up. Fifty-six had good results and were considered cured. Twelve were definitely improved but not completely free of symptoms, and in 5 symptoms recurred with hernia proved by x-ray studies. No operative deaths occurred from primary hernial repair.

SUMMARY

A brief discussion of esophageal hiatal hernia has been presented. Surgical repair of the hernia is considered the best method of treatment for patients with symptoms. Emphasis is placed on examining for strictures and mucosal rings at the time of surgery by performing a gastrotomy and inserting the index finger into the lower part of the esophagus.

Eighty-four operative cases are reported. In 11 of these a phrenic nerve crush was performed; in 73, primary repair of the hernia.

The results were good in 56 cases, improved in 12, and in 5 there was a recurrence of symptoms and hernia as proved by x-ray examination.

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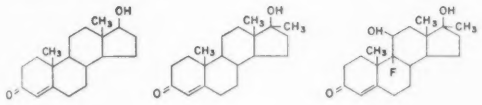
TREATMENT OF ADVANCED BREAST CANCER WITH FLUOXYMESTERONE (HALOTESTIN)

VICTORIA L. BECKETT, M.D., and MICHAEL J. BRENNAN, M.D., Detroit, Michigan

THIS REPORT concerns our experience with 23 cases of carcinoma of the breast with metastasis, treated with the oral androgen 9 alpha-fluoro-11 beta-hydroxy-17 alpha-methyltestosterone or fluoxymesterone (halotestin). The structural formulas of testosterone, methyltestosterone, and fluoxymesterone follow:



Testosterone | 17-Methyltestosterone | Fluoxymesterone

METHOD

Selection of patients. Twenty-three patients with advanced metastatic breast cancer were treated between January 1956 and May 1958 by our service. In all but 1 patient there had been histologic verification of carcinoma of the breast. In 20 patients the diagnosis had been made at the time of mastectomy, and in 2 from tissue examination of metastatic lesions. In the 1 instance of no histologic verification there was the obvious history of an enlarging lump in the breast for 2 years with subsequent appearance of skin nodules and enlarged lymph nodes. When the patient first came to us, x-ray evidences of lung and bone lesions were also present.

Almost all the patients had had previous therapy for the disease. All except 3 had undergone some form of mastectomy as the initial treatment. These 3 all presented inoperable lesions, and 2 of them were given x-ray treatments to the breast. When recurrence took place among the mastectomy cases, all who were menstruating or near menopause had undergone bilateral oophorectomy. For those well past menopause, or for postoophorectomy cases, progression of disease was then treated by androgen, hypophysectomy, or cortisone, in any order. Fluoxymesterone was used as the androgen in this stage of our program in these 23 cases.

The average age of these patients at the time of histologic diagnosis was 51 years. The age range was from 35 to 63 years.

The average time for starting fluoxymesterone was 31 months after diagnosis; the range was from 1 month to 6 years after diagnosis. The single exception was the case of a woman who had a recurrence in the breast 25 years after simple mastectomy. Fluoxymesterone administration was started 4½ years after recurrence.

Dosage of drug. We considered 15 to 30 milligrams daily for 1 or more months as an adequate trial dosage of this drug. Fifteen patients were so treated. Four others were considered probably to have had an adequate amount of this drug, for although the dosage was low (2.5 to 15 mgm. daily) they had been receiving it for 6 or more months. Thus there was a total of 19 patients who had had a significant trial of the drug.

Four patients had insufficient medication for the following reasons: in 3 there was rapid progression of disease and in 1 uncomfortable side effects so that the drug was stopped early. These 4 are considered among our failures.

RESULTS

Remissions and failures. An objective remission is defined as an instance of diminution in size of at least 1 measurable lesion

From the Oncology Division of the Henry Ford Hospital, Detroit, Michigan.

TABLE I.—CASES OF OBJECTIVE AND SUBJECTIVE REMISSION

	Age (yrs.) at menopause	*Previous treatment*	*Age at fluoxymesterone treatment*	*Lesion improved*
M.G.	46 (surgical)	Radical mastectomy (age 53) Hypophysectomy	57	Lung
A.G.	43 (natural)	Simple mastectomy (age 37) Testosterone enanthate	68	Lung
M.De.	50 (natural)	Partial mastectomy (age 63)	65	Skin, bone
E.L.	53 (natural)	Simple mastectomy (age 50) Oophorectomy (age 54) Testosterone propionate Hypophysectomy	56	Bone
M.Do.	43 (natural)	Radical mastectomy (age 50) Testosterone propionate	52	Lung

TABLE II.—CASES OF OBJECTIVE ARREST, SUBJECTIVE IMPROVEMENT

	Age (yrs.) at menopause	*Previous treatment*	*Age at fluoxymesterone treatment*	*Lesion unchanged*
L.S.	42 (surgical)	Radical mastectomy (age 59) Testosterone enanthate	62	Lung
M.S.	51 (natural)	Radical mastectomy (age 60)	62	Skin

TABLE III.—CASES OF OBJECTIVE AND SUBJECTIVE WORSENING

	Age (yrs.) at menopause	*Previous treatment*	*Age at fluoxymesterone treatment*	*Lesion worse*
R.F.	43 (surgical)	Radical mastectomy (age 43) Oophorectomy	45	Bone marrow
M.N.	48 (natural)	Radical mastectomy (age 59)	64	Pleura
E.Z.	54 (natural)	Radical mastectomy (age 53) Dienestrol Oophorectomy (age 57) Testosterone propionate	57	Bone
P.P.	47 (natural)	Simple mastectomy (age 57)	57	Liver
M.R.	50 (surgical)	Radical mastectomy (age 48) Oophorectomy Cortisone Testosterone enanthate Hypophysectomy	51	Bone
V.D.	50 (surgical)	Radical mastectomy (age 48) Premarin Oophorectomy Simple mastectomy (other side) Hypophysectomy	53	Liver

while none of the others show progression. A subjective remission means general improvement in the sense of well-being, decrease in uncomfortable symptoms, and increase in appetite, weight, and activity.

Of 23 patients, 5 had both objective and subjective remissions lasting 3 months to 1 year and 5 months. Surprisingly, 2 of these 5 were posthypophysectomy cases. (There was a total of 4 posthypophysectomy patients on whom we tried fluoxymesterone in this study.) In addition to these 5 patients, 2 had arrested lesions while continuing to feel well for a period of 11 months to 1 year and 2 months. One of these maintained an objective remission which had started with administration of an injectable androgen—testosterone enanthate. These were probable cases of arrest and are included in the remission group which then totals 7 (or 30 per cent) of our group of patients.

Sixteen patients (or 70 per cent) were classed as failures although 6 of these were subjectively improved for from 3 weeks to 3 months. One patient among these 6, who

was observed for 4 months and subsequently lost to follow-up, experienced subjective improvement for about 1 month at the end of these 4 months, but had no roentgenograms to document changes in the bone lesions which were her only recurrences. In the other 5 cases there was objective progression during the period of subjective improvement. Ten patients constituted frank failures with objective worsening without subjective improvement or the drug had to be stopped because of side effects.

In trying to analyze the remission group we could not come to any conclusions as to why this group of patients was so favored. The number of patients, of course, is very small.

Unfortunately, gonadotropin estimates were available in only a few cases before and during fluoxymesterone therapy. However, the 4 estimates which we did have proved extremely interesting. These were all from patients in the remission group; 2 of whom had undergone previous hypophysectomy and 2 had not.

1. Patient M. G. had shown a fall of gonadotropin titer from +64 to 0 after hypophysectomy, and prior to fluoxymesterone therapy. Her gonadotropin titer remained 0 after regression developed with use of the drug.

2. Patient E. L. did not have gonadotropin values taken before or immediately after hypophysectomy. Later, during treatment with fluoxymesterone, her gonadotropin was 0. On the same date, her protein bound iodine (PBI) was at myxedematous levels. Therefore, we think the zero gonadotropin value probably resulted from a complete hypophysectomy rather than from the fluoxymesterone therapy.

3. Patients M. D. and L. S. both had high gonadotropin titers of +64 prior to and during fluoxymesterone therapy. If these 2 cases are indicative, it would seem that this drug does not suppress gonadotropin to any major degree.

We will discuss these findings further later in this article.

Side effects. There were 2 or possibly 3 instances of side effects of a serious nature other than masculinization. One patient had polycythemia, twice necessitating phlebotomy of 500 cubic centimeters each when the hemoglobin reached 18.4 grams. She was patient L. S. in Table II, and her hemoglobin had started to rise after testosterone enanthate therapy was started and before fluoxymesterone was given.

In 1 patient jaundice and hepatomegaly developed and on biopsy biliary stasis was demonstrated. The liver size regressed and jaundice disappeared after fluoxymesterone administration was stopped. There was some question as to whether this could have been produced by promazine which she had taken intermittently until 2 weeks before the onset of jaundice. However, as the doses of promazine were small (25 mgm.) and intermittent, whereas the 30 milligrams of fluoxymesterone had been taken regularly daily for 5 weeks prior to the appearance of liver disease, fluoxymesterone is the more likely culprit.

The third patient was one who died of a fulminating hepatitis about 5 weeks after taking 30 milligrams of fluoxymesterone daily. Serum transaminase was 360 units per cubic centimeter. No autopsy or liver biopsy was obtained to verify the cause of this hepatitis. She had been given 3 pints of blood at the nailing of a pathologic fracture of the femur 2½ months before, and this case could well have been one of serum hepatitis rather than fluoxymesterone hepatitis. Before the administration of fluoxymesterone was begun, the liver was not palpable, liver function had been normal, and metastatic disease was thought to be confined to bone alone.

Masculinization appeared in almost all patients given an adequate trial of the drug. This was minor and mostly limited to deepening of the voice and mild hirsutism. Clitoral hypertrophy and increased libido was notable in 6 patients. Compared to changes from the administration of 100 to 200 milligrams of testosterone enanthate

every week, masculinization was much less, and edema was minimal. Since these two drugs were both on trial on our service at about the same time, a few patients had been switched from testosterone enanthate to fluoxymesterone therapy, and thus we could compare the masculinizing effects of the two drugs in the same patient.

Other side effects were minor and difficult to differentiate from symptoms of progression of disease. These included nausea, vomiting, diarrhea, edema, and increased pain. We had no other case of clear-cut increased hemoglobin. There was no symptomatic hypercalcemia.

DISCUSSION

Methyltestosterone has hitherto been the only oral testosterone with good suppressive effect on breast cancer. The doses necessary have been large, 50 to 200 milligrams daily. Lyster and associates have shown in castrated immature rats that fluoxymesterone was roughly 10 times as androgenic and 20 times as strong in protein anabolic effect as methyltestosterone.

Kennedy (3) has reported 29 cases of breast carcinoma in which he used this drug. Fifty per cent of his patients showed objective remission. Results in our series are closer to the 25 per cent regressions commonly observed with other androgenic agents.

The fact that in 2 of our cases remission occurred in posthypophysectomy patients is of both practical and theoretic interest. This means that we do not have to consider hypophysectomy as the last measure in palliation but may yet use an androgen when hypophysectomy fails. It has been postulated that a mechanism of action of androgen in the suppression of breast cancer may be that of depression of gonadotropin or that estrogen is antagonized peripherally. The fact that remission occurred in our hypophysectomy cases (1 with proved absence of gonadotropins) as well as in cases of continued high gonadotropins suggests that depressing gonadotropin is certainly not the only mechanism by which androgen acts on breast cancer.

We found fluoxymesterone effective in doses which are modest in their virilizing action. Troublesome edema did not occur nor did dangerous hypercalcemia, in contrast to testosterone propionate. This may be because our study group is very small. We consider it unlikely that larger doses will yield a greater number of remissions although this opinion has yet to be verified.

Fluoxymesterone jaundice has not been reported before. In our small series, there was 1, and possibly 2 such cases. This drug may be expected to resemble methyltestosterone in some of its toxic manifestations since it is also a 17 alpha-methyl androgen. Methyltestosterone like chlorpromazine has been reported by Kaplan to cause intrahepatic obstructive jaundice, such as was shown by 1 of our patients.

The reaction in the liver to these two drugs is deemed to be due to individual hypersensitivity. Moreover, a rare toxic hepatitis indistinguishable from other types of acute hepatitis has been reported with chlorpromazine by Kelsey and associates and could, therefore, apply to a 17 alpha-methyl androgen also. In such an acute hepatitis, serum transaminase can become very high. We believe that fluoxymesterone was not responsible for jaundice in our case of fatal hepatitis, although a toxic hepatitis due to the drug cannot be absolutely ruled out.

Kennedy and Gilbertsen (4) noted increased erythropoiesis in patients receiving large doses of androgens. This was strikingly borne out in our patient in whom sufficiently severe polycythemia developed to require venesections.

In our study, the wide discrepancy between the subjective and objective responses to androgen therapy was noted. This observation has been made by Lewison and associates and discussed by Nathanson. Thirteen patients felt subjectively better with fluoxymesterone therapy, although only 7 of them showed objective improvement or arrest.

CONCLUSION

A new oral androgen has been found to be effective in suppressing advanced mammary cancer in postmenopausal patients. Remission occurred in 7 (30 per cent) of our 23 patients—in 2, after hypophysectomy. Fluoxymesterone appears to be less masculinizing than injectable androgens in therapeutic doses. It can cause liver dysfunction such as seen with methyltestosterone.

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EDITORIALS

THE INOPERABILITY OF INFLAMMATORY CARCINOMA OF THE BREAST

NORMAN TREVES, M.D., F.A.C.S., New York, New York

A RECENT EDITORIAL in this journal (2) has prompted the writer to express views which are at variance with the substance of the opinions enumerated.

The term inflammatory carcinoma of the breast was suggested as early as 1922 by Lee (4) to describe the most malignant clinical form of breast cancer. Since this designation was proposed by two members of the Breast Service at Memorial Hospital in 1924 (5), first describing more than a score of patients exhibiting such a type of mammary carcinoma, it seems proper that one of the surviving authors, still greatly interested in this variety of malignant breast neoplasm, should reply to the editorial in this journal where, incidentally, the first significant report on this disease was published. The views expressed are those held, we believe, by a minority of surgeons who object to classifying inflammatory breast cancer as inoperable.

Before replying to this provocative expression of opinion, it is first in order to propose a clear definition of the lesion about which the question of inoperability has been raised. The following is from the original clinical description of the lesion:

> The rate of growth is startling in its rapidity and often fills the entire breast in a few weeks. . . . The overlying skin is reddened and brawny and this blush may extend far beyond the limits of the mammary gland. . . . The axillary nodes of the corresponding side become involved early, increase rapidly in size, and are unusually bulky. . . . As the disease progresses the skin becomes deep red or reddish purple in color and to the touch is brawny and infiltrated. *The inflamed area presents a distinct raised periphery after the fashion of erysipelas.* The infiltration is so marked that the examiner, with his eyes closed, in passing the hand over the skin can distinguish readily the sharp contrast between normal and affected tissue. The redness may extend far beyond the normal confines of the breast, in some instances reaching from the sternal region in front, completely around one-half of the chest to the mid-line behind, or extending downward over the upper portion of the abdominal wall. . . ."

In summation, this form of cancer occurs with brawny (edematous) induration of the skin which is deep red or reddish purple in color and the edge of the discoloration is raised after the fashion of erysipelas. This is the advancing edge of tegumental involvement and produced by the solid strands of cancer cells invading the blood and lymph channels of the subdermal and subcutaneous tissue. One must here indicate that other forms of mammary carcinoma may produce an erythematous blush and edema of the skin and may lodge growing cancer cells in lymphatics and venules and even emboli in the deeper vessels of breast tissue, but these do not present the picture of a growing edge of subdermal involvement which simulates erysipelas. In other words, not all breast cancers which produce erythema are

From the Breast Service, Department of Surgery, Memorial Center for Cancer and Allied Diseases, New York.

inflammatory carcinomas. Why the integument reacts in this fashion is not to be explained on the basis of a toxin nor accompanying bacterial infection but probably is due to lively venous congestion; quoting Chris, "the peculiarly malignant nature of these inflammatory carcinomas in some manner induces hyperemia of the skin." The massive invasion of the derma and the subdermal vessels produces the well defined edge of the hyperemic induration. But even beyond this edge of erythema malignant cells may be demonstrated in blood and lymph vessels below the skin. These findings explain the failure of surgery in practically all instances, since any mastectomy incision passes directly across involved venules as well as lymphatics. For this reason, operation is usually followed by prompt local recurrence.

Most surgeons familiar with this form of breast cancer agree that its incidence is about 2 per cent but few agree that the treatment "is controversial." Why should surgery continue to be used for the treatment of a condition which admittedly "is a deadly disease and almost all patients who have it die within a short time" (2)?

Haagensen at the Presbyterian Hospital reported that of 56 patients with inflammatory carcinoma 29 had radical mastectomy. All died, with an average survival of 19.5 months postmammectomy and a total average duration of disease of 25.9 months. Of the 27 treated by other methods (usually roentgen therapy) the average survival was 10.1 months and the average survival from first symptom was 13.6 months. These data fail to make a case for those advising radical mastectomy for this type of breast cancer since it seems apparent that the reason the former group lived longer was not the result of surgery per se but was due to the fact that the patients were probably treated earlier in the course of disease. None in this group of 29 patients survived 5 years. It is likewise obvious why the 27 patients treated by other means survived for significantly shorter periods. Either their disease was farther advanced when seen and they could not be operated upon, or their lesions were clinically more aggressive. One must agree with Haagensen's conclusions (and ours which were advanced in the year 1924) that "when no cures can be expected, and no definite evidence of prolongation of life can be shown it seems entirely unreasonable to treat these patients by radical mastectomy."

In attempting to make a case for radical mastectomy as the treatment for inflammatory breast cancer, the editorial contains statements which appear to be at variance with the accepted concepts of this form of disease. It is admitted that "the disease is so lethal that the best treatment will be hard to justify." We hope to convince others that radical mastectomy for mammary carcinoma of this type, in the light of past and present clinical experience, is contraindicated. One exception to this admonition stating that surgery should be reserved for those patients "with a localized form of the disease," should be rejected since this disease is notoriously unlocalized! Aside from the report by Meyer, Dockerty, and Harrington, who performed radical mastectomy on 61 of 74 patients in whom inflammatory cancer was diagnosed, all other surgeons have been much more timid in resorting to radical breast surgery as the primary treatment for this condition. The data of Meyer and his associates leave doubt that they were operating upon true inflammatory carcinoma since erythema was recorded in only 73 per cent of their patients.

Based upon a fairly recent report, this editorial has stated that other material from the literature as well as their own (7) leaves the question still undecided concerning the operability of inflammatory cancer of the breast. But there is the admission that it is a highly lethal form of cancer, refractory to almost all forms of treatment.

Let me summarize the data in chronologic order that were available at the time the editorial was written:

Year		No. of cases	Radical mastectomy	5 year survival
1924	Lee and Tannenbaum.	28	4	0
1938	Taylor and Meltzer	38	6	0
1948	Meyer, Dockerty, and Harrington.	74	61	3
1950	Chris	20	4	0
1956	Rogers and Fitts.	46	10	1
1956	Haagensen	56	29	0

In these 6 reports a total of 262 cases of inflammatory carcinoma of the breast was diagnosed. In 114 cases, about 44 per cent of the total, radical mastectomy was performed. In the entire group, 4 patients survived free of disease for 5 years or more (1.5 per cent); while the percentage survival of those operated upon was 3.5 per cent. Surely this is a woefully small figure from which to obtain justification for radical surgery in this admittedly lethal form of malignant neoplasm of the breast. Besides, in the summary given, there seems justifiable doubt that some of these patients had true inflammatory carcinoma of the breast.

No one gainsays the futility of surgical procedures for those patients in whom inflammatory cancer recurs after surgery or those in whom disease recurs in the inflammatory phase after radical surgery upon a tumor which had none of the clinical features of this type of cancer at the time of surgery, or for the inoperable patient with visceral or osseous metastases. It is only the occasional case which will tempt the surgeon to proceed with radical breast surgery for a form of neoplasm of questionable operability in the hope that the fates will be kind to his unfortunate patient. For he knows full well that in the face of present statistics his efforts will probably be unsuccessful. It has been stated that "a few of these patients may be helped by operation." How are these few to be chosen and especially those with a "localized form of disease"? This is a form of cancer of the breast noted for early and wide dissemination. Let us face the fact that here is a form of breast cancer that offers notoriously poor results by surgery while the over-all 5 year clinical cure rate for the average case is about 45 per cent.

As John Locke wrote in 1687, "the degree of assent we give to any proposition should depend upon the grounds of probability in its favor."

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AN EVALUATION OF THE FEMORAL HEAD PROSTHESIS AFTER TEN YEARS OF EXPERIENCE

MARK B. COVENTRY, M.D., F.A.C.S., Rochester, Minnesota

THE BROTHERS JUDET of Paris published their article on the utilization of a femoral head prosthesis in the reconstruction of the hip in 1949. The procedure was rapidly adopted by orthopedists throughout the world. The evolution of this procedure has seen its use ultimately crystallized so that today there is no great difference of opinion as to its indication in avascular necrosis of the femoral head, in certain ununited fractures of the femoral neck, and in arthroplasty of the hip in both degenerative and rheumatoid arthritis. Its merit in the treatment of these conditions has been proved and, undoubtedly, it will continue to be a most useful adjunct in the rehabilitation of certain patients with disease of the hip.

There has been evolution also in the construction and design of the prosthesis. Literally dozens of different styled prostheses have been used. In general, the trend is away from the stem-type prosthesis originally described by the Judets and toward an intramedullary type of prosthesis; it is away from plastics, such as the original acrylic prosthesis and later nylon, and toward the use of metal, either stainless steel or vitallium. Breakage has been almost eliminated by the use of metal. Loosening of the stem prosthesis, formerly a common occurrence, has been largely overcome by the intramedullary nature of the prosthesis.

The use of a femoral head prosthesis in the treatment of fresh fractures of the femoral neck is still controversial. Some orthopedists believe that the complications of the broken hip are so common and so disastrous that they use a prosthetic replacement in all patients with fracture of the femoral neck. Others rarely use the femoral head prosthesis for fresh fractures of the femoral neck. Perhaps the best use lies somewhere between these extremes; and as time goes on, indications for use of the prosthesis in the broken hip will become more clearly defined. Present experience leads to use of the prosthesis in fresh fractures of the femoral neck in the following circumstances:

1. Fracture of the femoral neck with dislocation of the head and comminuted fracture of the femoral head (or neck) which prevents adequate reduction.

2. Pathologic fractures, if the pathologic process is confined to the neck. Replacement with a prosthesis will enhance the patient's recovery and will allow earlier and less painful ambulation.

3. Fractures of the femoral neck which cannot be reduced adequately and fixed internally. It is generally conceded today that unless an accurate reduction of the fractured neck is obtained and unless that reduction is held securely with some type of internal fixation, a good result cannot be anticipated.

4. Fracture followed by an undue delay in attempted reduction, perhaps more than a week. It has been the experience of most surgeons that adequate reduction is difficult after such delay. Primary prosthetic replacement should be considered seriously for these patients.

5. Certain fractures which tend to show absorption at the fracture site and slipping or "falling apart" sometime after the reduction and fixation. These conditions probably develop because the fracture has not been reduced properly and held with internal fixation. Such fractures are indications for use of the femoral head prosthesis.

From the Section of Orthopedic Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Other methods, such as bone grafting, also are effective.

6. Fracture of the femoral neck in patients who undoubtedly will walk again if the femoral head is replaced by a prosthesis. There would be little or no indication for prosthetic replacement if one did not anticipate that the patient would ever walk again. Certain patients who have had severe strokes, or who are elderly and too feeble to walk, fit into this category. Certainly a successful nailing is preferable, in these patients, to an operation of the magnitude of inserting a femoral head prosthesis.

7. Fractures in patients who are in a particular age group. How does the patient's age affect indications for a prosthetic replacement? As yet no one knows whether the femoral head prosthesis will last indefinitely. I would therefore state, categorically, that it should be reserved for patients in the older age group, evaluating, of course, the physiologic rather than the chronologic age. In evaluating our experience with 30 patients at the Mayo Clinic in whom the prosthesis was used in fresh fractures, we found the average age to be 75.5 years.

Technically, the successful "nailing" for fracture of the femoral neck is, perhaps, more difficult than the insertion of a femoral head prosthesis. It may require more skill in reduction, in making and interpreting roentgenograms, and in accurate placing of the nail or pins. For this reason there may be some tendency to abandon conventional methods and to use the femoral head prosthesis more freely. I hope this will not happen and that the femoral head prosthesis will not be used simply as an expedient.

It might be said, then, that after 10 years of experience with its use, the femoral head prosthesis has some definite and clear-cut indications. One of these indications is fresh fracture of the femoral neck. Here, however, it should be used sparingly and only when reduction and internal fixation by usual methods are unsatisfactory. A continued attitude of conservatism regarding the selection of patients for this operation is warranted. The best result following femoral head replacement is never quite so good as the result following closed reduction, internal fixation, and healing of the fracture in excellent position.

THE SURGEON AT WORK

THE REPAIR OF TISSUE DEFICIENT HERNIAS BY AORTIC IMPLANTS

S. J. FOGELSON, M.D., F.A.C.S., and C. R. JACKSON, M.D., Chicago, Illinois

IT HAS BEEN reported by Pressman and Simon that lyophilized homologous aorta can be depended upon to close large defects up to 10 rings in length and half the circumference or more in the trachea of dogs. "These implants survived as aortic tissue for many months retaining their elastic tissue elements in a pattern closely approximating the normal often for periods as long as two years."

This report suggested that the elastic human aorta should prove an ideal framework for the surgical repair of tissue deficient hernia. It would serve as a scaffold for growth of sturdy white fibrous tissue which normally closes the hernial defect.

The implants were obtained from the artery bank of the Chicago Heart Association. The method of preparing these aortic grafts had been described by Milloy and Fell. The lyophilized aorta is soaked in an isotonic saline solution for 20 minutes. It is then incised longitudinally, and the resulting rectangular implant is ready to be sutured in place with the intimal surface facing downward. The implant covers not only Hesselbach's triangle but extends from the pubic spine, the periosteum of the pubic bone, the lateral border of the rectus, the white fascia of the internal oblique, the iliac spine, and finally to the shelving edge of the inguinal ligament. Suturing of the implant is usually started in the pubic bone area, and the implant is cut to fit the defect by repeated segmental trimming of the excessive aorta as the suturing progresses. The cord structures penetrate the graft through a triangular defect, from which a transverse incision extends to the lateral edge of the graft. This incision is resutured as the final step of implantation of the graft.

From the Department of Surgery, Northwestern University Medical School, Chicago.

CASE REPORTS

Six lyophilized aortic homografts have been used to reinforce the closure of the defects in 5 patients with tissue deficient inguinal hernias.

The first patient was operated upon in April 1958. A direct inguinal hernia on the left side could be closed satisfactorily by orthodox methods. A tissue deficient direct inguinal hernia was found on the right side; the neck of the hernial sac was approximately 7 centimeters in diameter. The transversalis fascia was tissue paper thin and infiltrated with lobules of fat. Orthodox repair resulted in undesirable tension on tissues despite relaxing rectus sheath incision. The end result of repair appeared inadequate. For this reason, it was reinforced by an aortic implant which was sutured in place with fine interrupted stainless steel. The postoperative course of this patient was uneventful. There was no local or systemic reaction, and when the patient was again examined on December 1, 1958, 8 months postoperatively, there was no evidence of recurrence.

The second patient was operated upon December 1, 1958 for a large direct inguinal hernia on the left side. The defect consisted of the entire inguinal floor. Orthodox repair consisting of high sac amputation and closure of the transversalis fascia defect was supplemented by an aortic implant. This patient tolerated the procedure well and also had no reaction.

The third patient had a very large direct inguinal hernia on the left side with extension of the sac into the scrotum; the sac contained many loops of small bowel. Here again, the deficient tissue available for repair seemed inadequate and an aortic implant was again used to cover the defect.

The fourth patient had a large inguinal hernia on the right side of 12 years' duration with extension of the sac into the scrotum. Orthodox repair supplemented by aortic implant was performed on November 6, 1958, and the same procedure was done for another large indirect inguinal hernia of the left side on November 20, 1958. This patient also made an uneventful recovery.

The fifth patient was a 76 year old male who had had an inguinal herniorraphy on the right side in 1908. A bilateral herniorraphy was done in 1925 because of a recurrence; a second recurrence promptly followed. On November 24, 1958, under local anesthesia, it was found that the left inguinal region contained a large direct inguinal hernia complicated by a large femoral hernia with displacement of the femoral vessels laterally; the inguinal ligament was absent. Extreme tissue deficiency rendered attempts at orthodox repair futile. An aortic implant covering these defects successfully retained the abdominal viscera in the peritoneal cavity and the previously existent large inguinal bulge was now absent. On the second postoperative day, the femoral hernia on the right incarcerated and emergency surgical therapy was required; this added unusual stress was well tolerated. The patient was discharged 4 weeks later; the aortic graft repair on the left side was excellent, whereas the femoral hernia on the right side had already recurred.

DISCUSSION

In each patient, an homologous aortic graft was used as an adjunct and not as a substitute for orthodox hernial repair. The implant was tolerated with neither local nor systemic reaction. These experiences suggest the use of homologous aortic grafts in other types of hernias such as umbilical and postoperative incisional hernias, which has been done.

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CORRECTION OF FISTULA OF STENSEN'S DUCT BY WIRE SETON

JAMES H. ERWIN, M.D., F.A.C.S., Mobile, Alabama

WITH THE EXCEPTION OF paralysis of the facial nerve or one of its major branches, external salivary fistula is the most distressing nonlethal complication of surgical procedures in or near the parotid gland. Although not a common lesion, it may be a source of discomfort to the patient as well as a trial to the surgeon. The patient's emotional and physical make-up may be subjected to varying degrees of stress during repeated and prolonged attempts at surgical correction. This is especially true if the fistula is not recognized as such.

In general, it may be said that methods of treatment of parotid fistula, especially those originating from Stensen's duct, have been unsatisfactory. Roentgen rays may be used to suppress secretory activity of the gland if the amount of glandular tissue is small. If there has been any previous x-ray therapy in this area, this form of treatment may be contraindicated. There is also the problem of obtaining proper and adequate radiation for patients who live a great distance from the source of therapy.

Silk worm gut, horsehair, silk, metals, and ureteral catheters have all been used as intraductal dowels to correct such fistulas. In some cases, the results have been good. However, a dowel can be expected to bring good results only when the two ends of the duct are close together.

Section of the auriculotemporal nerve with its parasympathetic fibers was formerly considered to be effective in decreasing salivation. Some have rejected this form of treatment. Banthine® has been suggested as a depressant to the parasympathetic fibers found in the nerve.

A more radical method has been suggested, namely, that of complete surgical ablation of the parotid gland and removal of the duct. However, radical removal would probably also cause severance of one or more major branches of the facial nerve due to the extensive inflammation and fibrosis surrounding the ductal area.

The successful use of a wire seton to repair a parotid fistula was reported by Fishler and Pogorel. In a review of the literature I was unable to find any other patient who had been so treated. Nevertheless, it was my belief that this same procedure might be applicable in the case described herein:

J. W. was admitted to the Mobile Infirmary on April 21, 1958, with a facial ulcer of 3 years' duration following drainage of an abscess in that area. The ulceration had been recurrent. It would heal spontaneously and then break open and drain. When the ulcer was healed there was some swelling of the parotid gland and tenderness in that area. When ulcerated, a fluid drained from the area but this was related to hard labor. He had been seen by a number of physicians and surgeons during these past 3 years. On one occasion, due to persistence of his complaints, he had been hospitalized in the State Mental Hospital. Several months later he had been seen at a large tumor clinic and the ulcer on the cheek impressed all of the examining staff as being factitious and was thought certainly to have been aggravated by the patient. However, he denied that he had ever deliberately opened the ulcerated area with a sharp instrument. Biopsy at that time revealed a nonspecific severe dermatitis with fibrosis. It was believed by most who saw him that no surgical procedure should be performed as a corrective measure, and the patient was admitted at this time for re-evaluation of his psychiatric background.

The next day, at consultation, a 3 centimeter, partly epithelialized ulcer with a bed of pale granulation was noted on the right cheek. In the center of the ulcer was an opening about 2 millimeters in diameter. When the patient would chew gum, saliva would pour from this opening in drops and run down the cheek. The same thing happened when the patient ate. The other salivary ducts were patent and saliva could be seen flowing from these ducts into the mouth. The right parotid duct was somewhat elevated and its opening was dry. A white caseous material could be expressed with a tongue blade from its distal 1½ centimeters. No saliva could be

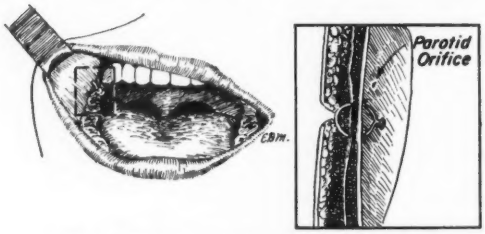

FIG. 1. Diagram of wire seton in position.

forced through this duct. Roentgenograms showed no evidence of stones in the right parotid duct. My impression of the clinical situation was as follows: Apparently, 3 years before admission, the parotid duct had been blocked by a stone or by some other debris. This caused salivary retention with secondary infection and abscess formation. The abscess was drained and as a result of the drainage or the damage done by the abscess, subsequent attempts at local therapy in addition to chronic inflammation had caused wide separation of the ends of the salivary duct. The psychiatrist believed that the mental situation was not severe and that there was no neurologic contraindication to surgical correction of this fistula.

On April 29, 1958, the patient was taken to the operating room. The technique followed was essentially that described by Fishler and Pogorel. The entire area around the fistula and the ulcer was infiltrated with 1 per cent procaine. The infiltration was carried through the entire thickness of the cheek. A U-shaped piece of No. 7 tonsil wire was inserted into the cheek so that the limbs of the wire straddled the external opening of the fistula. The two limbs were then passed completely through into the mouth so that they both appeared approximately 1½ centimeters from the old internal opening of the parotid duct. The ends of the wire were then twisted to prevent their slipping out (Fig. 1). The patient experienced no pain during this part of the procedure. Since the wire was passed through a chronically infected area it was thought best to give the patient the standard dose of tetanus antitoxin and a broad spectrum antibiotic. He was discharged that day on a regular diet and was given a prescription for one of the broad spectrum antibiotics.

The patient was seen again at the office 1 week after discharge from the hospital. Through some misunderstanding he had not taken the antibiotics as directed. Approximately 48 hours after discharge from the hospital he developed some fever, pain in the jaw, and some trismus. He was seen by his family physician in his home town and was started on one of the broad spectrum antibiotics. At this time there was still a slight tenderness of the cheek and he could not quite open his mouth completely.

By May 19 the swelling of the right cheek had subsided and the ulcer had healed so that there was a small loop of the wire protruding from the skin. Since the patient lived some distance away he was hospitalized, and the wire was tightened inside the mouth. The course of antibiotics was repeated and there was no difficulty at this time. He was seen in the office 1 month later and the wire was cut and removed through the mouth.

The skin had completely healed and since the insertion of the wire there had been no more external salivary drainage. During the next 6 months, the patient was seen on several occasions and at no time was he having any difficulty. On each occasion the new opening could be clearly seen and a free flow of saliva was present.

SUMMARY

A simple procedure, first described by 2 otolaryngologists, has been re-emphasized for correction of external salivary fistula of the parotid gland. General surgeons, especially those interested in the head and neck, may find it useful.

REFERENCE

1. FISHLER, H. W., AND POGOREL, B. S. Repair of parotid fistula. Arch. Otolar., Chic., 1955, 61: 331-332.

THE SURGEON'S LIBRARY

Reviews of New Books

AN EXTREMELY ACCURATE and well documented résumé of the Surgical Treatment of Mitral Stenosis by the classical closed approach is presented in the scholarly work by Helge Baden.[1] The book consists of a careful review of the world's literature on the development of mitral valvotomy, the prognosis of mitral stenosis, and the surgical treatment of mitral stenosis. The main portion of the book is devoted to a very careful analysis of 167 cardiotomies in 165 patients with a view to mitral valvotomy. A very careful review of the preoperative and operative data, diagnostic criteria, and findings at operation and follow-up studies are presented.

The book is particularly useful because of the care which the authors have exerted in analyzing the results of operation. Their own series is interpreted in the light of the reports of others which makes the book exceedingly valuable.

It is the opinion of the reviewer that this is one of the most comprehensive reports on this subject that has been presented. It is particularly pertinent at this time when surgeons all over the world are reviewing their techniques for the treatment of mitral stenosis and attempting to assess the results of the closed approach to mitral valvotomy. This is rendered, of course, pertinent by the availability now of open approaches to the mitral valve.

Careful study of this book is recommended to all serious students of the surgical treatment of mitral valvular disease. —*John W. Kirklin.*

SEVEN YEARS have elapsed since the publication of the first edition of Lichtenstein's treatise on bone tumors, a subject which has never ceased to engage the interest of many, as attested to by the appearance of 2 other textbooks published in this country within the past 2 years.

Lichtenstein's new edition of *Bone Tumors*[2] follows faithfully the general outline of the first with a few notable exceptions; i.e., he now employs the term benign osteoblastoma while formerly he preferred osteogenic fibroma of bone, so that the chapter which previously appeared under the latter heading has been eliminated. His reasons for this change seem sound to the reviewer.

A new chapter, "Tumors of Periosteal Origin," has been added which includes both benign and malignant tumors derived from the periosteum. Herein, Lichtenstein places the lesion which was originally described by Geschickter and Copeland as "parosteal osteoma" but which is now generally accepted as an osteogenic sarcoma of parosteal or juxtacortical derivation, although its low grade character and often long period of development prior to metastasis, are becoming well recognized. Lichtenstein believes that this tumor is of two types: those which appear malignant from the start, and those which have a slow evolution to a malignant lesion. It would appear to the reviewer that this tumor might well have been considered or referred to in the chapter on "Osteogenic Sarcoma."

It is gratifying to note that the author recognizes a tendency on the part of benign tumors of cartilaginous derivation to undergo chondrosarcomatous evolution. This has seemed to many to be a feature deserving of definite emphasis, especially since in the case of secondary chondrosarcomas a comparatively favorable prognosis may be expected if their true nature is promptly recognized and appropriate treatment (extirpation or ablation) is carried out.

Lichtenstein has become convinced of the existence of Ewing's sarcoma as a distinct entity, one differing from primary reticulum cell sarcoma of bone; and it is gratifying to note that he now approves of irradiation rather than amputation as the treatment of choice for both types. With increasing recognition of the fact that both of these neoplasms show marked local response to adequate doses of roentgen therapy, it is hoped that the number of unnecessary amputations will be diminished.

It would appear that since the publication of the first edition of his book the author has become convinced of the existence of primary liposarcoma. While general agreement on this point is lacking, it is possible that time and further study will provide a clarification of the question.

The author is to be congratulated on the choice of illustrations which, in this edition as in the first, are excellent, as are the reproductions of roentgenographic and histologic material as well as the format of the entire book.

While this book written by a pathologist is naturally

[1] SURGICAL TREATMENT OF MITRAL STENOSIS. By Helge Baden. 263 pages, 17 illustrations. 20 Danish kroners. Copenhagen: Store Nordiske Videnskabsboghandel, 1958.

[2] BONE TUMORS. By Louis Lichtenstein, M.D. 2nd ed. 401 pages, 220 illustrations. $12.00. St. Louis: The C. V. Mosby Co., 1959.

of particular interest to those working in this field—upon whom often rests the grave responsibility of establishing the correct diagnosis in lesions of bone—its appeal and value should not be regarded as limited to the pathologist but should include the orthopedic surgeon and the radiologist as well. This book will undoubtedly take its rightful place among the recent, notable texts published on the subject.

—Bradley L. Coley.

THE SEVENTH EDITION of Hamilton Bailey's single volume on *Emergency Surgery*[3] is a most fitting successor to the preceding editions which have been read and enjoyed since the first volume was published in 1930.

This book is a wonderful storehouse of practical information bringing together well indexed and reliable information on almost every contingency which may be encountered in the care of surgical emergencies. It is written as a text for those who must meet these emergencies, and, with few exceptions, one satisfactory method of handling each problem is described.

The present edition contains over 1,100 pages and is superbly illustrated with 1,576 splendid photographs and drawings, many of which are in color. The subject material is very clearly presented by systems, and increasing space has been given to diagnosis and differential diagnosis.

A large group of well qualified surgeons from the British Empire contributed to the volume either through preparation of a scientific chapter or a portion of a special section.

In this day when more and more of our surgical reading is, of necessity, spent with the great mass of current literature it is refreshing to find so much timely up-to-date information in a single volume for ready consultation.

This book will be of inestimable value to the surgical house officer and resident as they meet these surgical emergencies, which, in the words of the author, "arise at any hour." It will be most useful to the busy practicing surgeon for at his fingertips will be the substance of great experience in the management of these problems.

This volume should find an honored position in the library of all who are called upon to do emergency surgery. *—Charles W. McLaughlin, Jr.*

THE COMPACT VOLUME *Introduction to Surgery*[4] is well suited to its purpose, namely, to serve as a text for the second year introductory course in surgery at the College of Physicians and Surgeons, Columbia University. The fourth edition follows the pattern of the previous works but has been brought up to date by revision of certain sections and additions to what are termed functional considerations in surgery. These include sections on the heart and great vessels, peripheral circulation, and endocrine influences in surgical convalescence.

The contents encompass the whole of surgery beginning with historical contributions and going on to consider basic considerations such as injury and inflammation, repair, etc.

The authors have found it possible to reduce complicated subjects to their simplest terms in a very readable fashion. Some oversimplification, as for instance in the consideration of the sequelae of tenosynovitis, has resulted, but in general basic principles have been followed very well. In the sections on wounds it might have been possible to give a little more consideration to the role of tetanus prophylaxis, as well as the treatment of puncture and human bite wounds.

It is always possible to suggest possible additions; however, with the increasing role of the emergency service and need for efficient treatment of the acutely ill and injured patient it might be possible to include in later editions some fundamental principles of emergency room care.

The volume is of a handy size and easy to read. The illustrations, while not numerous, depict certain principles quite clearly. *—John H. Schneewind.*

IN TURELL'S two volume work entitled, *Diseases of the Colon and Anorectum*,[5] he has created a practical, progressive, and complete, though not encyclopedic, textbook on the function and diseases of the colon and anorectum.

The contributors are 82 well known authorities, most of whom are surgeons, but among the authors the following specialties are represented: dermatology, anesthesiology, urology, radiology, gastroenterology, pathology, gynecology, and proctology.

Sixty chapters are organized into 6 parts as follows: Part 1, Applied Basic Sciences; Part 2, Diagnosis; Part 3, Anesthesia; Part 4, Colorectal Lesions; Part 5, Anorectal Lesions; and Part 6, Special Considerations.

The chapters on anatomy and pathology and the chapters on surgical procedures have been profusely illustrated and the quality of these illustrations is excellent.

It is impossible, in a short review, to do justice to the many outstanding features of this book. The reviewer liked particularly the discussion of the cancer potential of adenomas of the colon and rectum in the chapter by Turell and Brodman (page 326). This is a controversial subject and is discussed succinctly and completely. Extreme views on this subject which have been published in the medical literature are presented. The practical approach to the problem of Turell and Brodman representing a middle-of-the-road position is given.

An excellent chapter by Southwick and Cole presents the recent work of Cole and others on anticancer compounds as adjuvants to surgery in the treatment of cancer and describes practical methods to prevent the dissemination of cancer cells during operative procedures. Also discussed in this chapter is the intriguing new work on cancer cells circulating in the blood stream and their significance.

[3] EMERGENCY SURGERY. By Hamilton Bailey, F.R.C.S.(Eng.), F.A.C.S., F.R.S.E. 7th ed. 1197 pages, 1576 illustrations. $32.50. Baltimore: The Williams & Wilkins Co., 1958.

[4] INTRODUCTION TO SURGERY. By Virginia Kneeland Frantz, M.D., and Harold Dortic Harvey, M.D. 4th ed. 335 pages, 13 illustrations. New York: Oxford University Press, 1959.

[5] DISEASES OF THE COLON AND ANORECTUM. Edited by Robert Turell, M.D. Vol. I, pages 1–608, Vol. II, pages 609–1238. Illustrated. $35.00 per set. Philadelphia and London: W. B. Saunders Co., 1959.

Repetition is a feature of multiauthored texts which taxes the capacities of students and of libraries. The repetition, however, seems to add to rather than detract from the over-all value of the material. Thus, the subject of electrolyte abnormalities is covered in the part devoted to applied basic science, and much the same material is presented again by another author in a chapter concerned with recognition and management of fluid and electrolyte disturbances complicating colonic surgery. One of these chapters is theoretic in approach and the other is practical. This material is omitted from most texts dealing with proctology, particularly in older books. The material is so important that the editor's decision to present it twice seems well justified.

With sufficient perseverance, a dedicated student can probably find something to criticize even in a work as excellent as Turell's. The present reviewer studied these volumes for a long time before he found a deficiency. The indications and technique of pelvic and groin lymphadenectomy as applied to the treatment of neoplasms of the anorectal region are not discussed. Perhaps also, the technique of pelvic exenteration should be given, as it is referred to in several sections of the text. Deficiencies of this nature are probably inevitable in a multiauthored work, and perhaps they will be remedied in succeeding editions.

The reviewer also wished that the subject of selection of operations for neoplasms of the anus had been dealt with as thoroughly as the selection of operations for carcinoma of the colon in the chapter by Peter Rosi. This is a subject about which the surgeon occasionally needs advice and its inclusion would increase the usefulness of the book.

Complete and detailed information on proctologic techniques of examination, instruments and instrumentation, techniques of radiotherapy, diets, surgical techniques and their results, and many other things enable this text to serve as a practical handbook as well as a complete reference work. It will be a valuable addition to the library of those who are interested in diseases of the colon and anorectum.

—*Frederick W. Preston.*

ONE DIFFICULTY in the production of a book on the hand is that during the past 15 years considerable literature has accumulated on this subject, stimulated by the repair of injured hands in World War II. A conspicuous feature of *The Hand*[6] is that the author has endeavored to distill from this literature the significant and salient material, and to present this in a simple concise manner.

The book consists of sections on anatomy, infections, trauma, medical diseases of the hand, and reconstructive surgery. The subject matter is presented in a straightforward and readable style. Of special interest are many black and white photographic reproductions, considerably enlarged, showing special details of trauma or pathologic conditions of the hand or fingers. There are also many reproductions of original drawings and roentgenograms illustrating the conditions described.

While one might differ on details of subject matter or matters of emphasis, the general principles presented are sound. This new book is a worthwhile contribution, and should be especially valuable to those doing general surgery and to those in their surgical training. The extensive bibliography available at the end of each chapter will be a ready key to the storehouse of literature on the anatomy and diseases of the hand.

—*Julian M. Bruner.*

A MOST UNUSUAL SURGICAL PRODUCTION is entitled *An Atlas of Surgery*.[7] It consists of 363 pages, 8 by 13 inches, containing 1,292 illustrations. It is almost entirely pictorial in nature, there being no text as such, but instead numerous inserts in the form of paragraphs or phrases to identify and elaborate upon the illustrations. Of necessity, the presentation of each topic was made extremely brief because of the magnitude of the attempt to be all inclusive. In fact, one criticism of the work is that very factor, since mere inclusion of certain topics serves to remind the reader of the scanty treatment afforded in other isolated instances.

The collection represents an amazing breadth of detail for certain portions of the book, and the photographs are nicely balanced with clear and quite accurate anatomic drawings. There are 8 sections, titled: Abdominal Surgery, Urology, Gynecology, General Surgery, Special Surgery, Orthopedics, Management of Operations, and Surgical Pathology. Many of the illustrations are original with the author, but many also are carefully credited to other sources. It is somewhat amusing to the American surgeon to note almost no references to American authorities, except under the section on heart surgery, in which certain pioneering American efforts are recognized.

The experienced surgeon may wonder at the motivation for such a tremendous effort of authorship, but he may well wish that in his formative years such a work had been available. For the student and the resident surgeon frequent reference to the book would seem an obvious short cut, and unquestionably the pictorial method has no peer in teaching. Students of nursing would do well to refer to the book often, as it makes clear the objectives of certain surgical efforts. However, in the preface, the author emphasizes that the book is no substitute for the standard textbooks and surgical journals but is simply an aid to consolidate practical knowledge with that from didactic lectures and library reading. Whereas the experienced surgeon might not feel compelled to add this book to his library, the young surgeon in his training period would seek far before locating a better method for quick and frequent review.

—*Edward S. Judd.*

IN THE THIRD EDITION of *Surgery of the Stomach and Duodenum*,[8] Welch has elaborated on the previous editions and included significant advances in surgery of

[6] THE HAND; ITS ANATOMY AND DISEASES. By John J. Byrne, M.D. 384 pages, 166 illustrations. $10.50. Springfield, Ill.: Charles C Thomas, 1959.

[7] AN ATLAS OF SURGERY. By F. Wilson Harlow, M.B., B.S. (Durham), F.R.C.S.(Eng.). Foreword by Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., D.Sc., F.R.C.S. 363 pages, 1292 illustrations. $8.50. New York and London: Grune & Stratton, Inc., 1958.

[8] SURGERY OF THE STOMACH AND DUODENUM; A HANDBOOK OF OPERATIVE SURGERY. By Claude E. Welch, M.D., D.Sc.(hon.). 3rd rev. ed. 405 pages. Illustrated by Muriel McLatchie Miller. $9.75. Chicago: The Year Book Publishers, 1959.

the stomach and duodenum. Again, there are excellent illustrations arranged in sequential manner which are useful as a guide to the various procedures. A brief text accompanies the illustrations and, in addition to providing a commentary, gives a critical evaluation of the usefulness of the procedure. Sections of the book embrace the anatomic, preoperative, postoperative, and anesthetic aspects of gastric and duodenal surgery. Special attention is devoted to hemorrhage of the upper gastrointestinal tract due to portal hypertension. There is adequate coverage of the common and important procedures utilized in surgery of the stomach and duodenum and, in most instances, more than one choice of procedure is available.

The book is designed as a handbook of operative surgery embracing the area of stomach and duodenum and will be of special value to the younger surgeon or surgeon in training. It can be highly recommended for this purpose. —*W. Harrison Mehn.*

THERE HAS LONG BEEN NEED for a comprehensive reference book on spontaneous and induced tumors in experimental animals. Stewart, Snell, Dunham, and Schlyen of the National Cancer Institute have now satisfied this need in admirable fashion in fascicle 40 of the *Atlas of Tumor Pathology*.[9] The fascicle opens with an historical review of transplantable and transmissible tumors of animals followed by brief sections on the sources of transplantable tumors, the techniques of transplantation, and the results obtained followed by detailed considerations of tumors of the various organ systems, for example, skin, subcutaneous tissue, muscle, bone, and endocrine glands.

Pathologic descriptions of some 50 transplantable and transmissible tumors of animals are included together with accounts of their natural history. Thirty are of mice, 10 of rats, 3 of rabbits, and 2 each of the dog and the chicken and 1 of the hamster, guinea pig, and frog. Not all experimentally induced tumors have been described, but the authors have selected representative examples. They have also considered the effects of hormones and the relations of the endocrine glands to the tumors mentioned and to other experimentally induced tumors.

The fascicle is illustrated by beautifully reproduced gross photographs and photomicrographs. Some of the latter are in color and are the most successful of those which have appeared in the other fascicles.

This fascicle will obviously be of chief interest to experimental investigators. For them the book will no doubt become a reference to which they will have frequent recourse. The book should also satisfy the curiosity of other readers who desire relatively brief accounts of these animal tumors. Again, attention is called to the fact that these fascicles give extremely good value for the money which is asked for them.

—*William B. Wartman.*

[9]ATLAS OF TUMOR PATHOLOGY. Section XII—Fascicle 40, Transplantable and Transmissible Tumors of Animals. By Harold L. Stewart, M.D., Katharine C. Snell, M.D., Lucia J. Dunham, M.D., and Samuel M. Schlyen, M.D. Published by the Armed Forces Institute of Pathology Under the Auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences—National Research Council. 378 pages, 287 illustrations. $3.50. Washington, D. C.: Armed Forces Institute of Pathology, 1959.

THE FIRST of a six volume series on *Cancer*[10] with an index on the subject introduces the purpose and expresses the anticipated end. The editor is Ronald W. Raven, an eminent British surgeon. Although the contributors are predominantly from the United Kingdom, there are chapters from some of the best students of neoplasms in this country.

In Volume I, Part 1—*Research into Causation*, the format is rather similar in the respective chapters. Surprisingly, the editor has allowed complete freedom and has inserted no comment. There is a definite trend toward conservatism and although many theories are advanced concerning etiology, no emphasis is placed on any one factor. Conclusions based on animal experimentation are not necessarily applied to man.

The individual sections are, at times, lengthy but not boring. Much use is made of graphs and tables which are clear. The photomicrographs are reproduced nicely, despite the fact that some are of high magnification.

A short account of the history of cancer is given at the beginning of the work. This is followed by material on the incubation period of cancer in man and carcinogenesis with a separate report on cholesterol. The biochemistry of cancer induction with chemical mechanisms of normal and abnormal cell division in reverse order are next. The next 6 chapters deal with hormones, viruses, nutrition, genetics, environmental factors, and radiation. Although much of this is theory, it behooves the person who is truly and vitally interested in the field to read these subjects diligently. If time does not allow, and particularly if there be a wish to study the later volumes, for a more practical approach, the discussions and the conclusions at the end of each section may be utilized. Each author has summarized the section and included many of his own thoughts.

Some quotations may be helpful: "Cancer is older than the literature of medicine," W. R. Bett; "The relations of diet to cancer are by no means simple," E. L. Kennaway; "The study of carcinogenesis is full of paradoxes," P. R. Peacock; "There is reason to believe that all of the methods of producing liver cancer may work through a more or less common mechanism," A. Clark Griffin; "The partial control of advanced prostatic carcinoma in man by castration and by oestrogenic compounds represents the most important advance in the treatment of disseminated cancer since the discovery of roentgen rays," Michael B. Shimkin.

Because of recent publicity in this country, the review on viruses as causative agents in cancer is most profitable reading. A similar comment may be made concerning radiation. The one on genetics is very apropos for any who concern themselves with this approach. P. C. Koller utilizes an appropriate quotation from J. V. Neel in a statement, "Many of the conclusions derived from experiments with Drosophila and mice, such as the role of natural selection, cannot be interpolated because man is neither an overgrown fruit fly nor an oversized mouse."

[10]CANCER. Edited by Ronald W. Raven, Q.B.E.(Mil.), T.D., F.R.C.S. Vol. I Part 1. RESEARCH INTO CAUSATION. 558 pages, 94 illustrations. $18.00. London: Butterworth & Co., Ltd., 1957.

In the chapter on "Environmental Factors," W. C. Hueper in 2 separate listings presents the various reasons now being offered as indicating a direct relationship between the markedly increased incidence of lung cancer with cigarette smoking and his own basis for being skeptical of such ready acceptance of unscientific interpretation.

In general, this is a good volume, clearly printed even though the paper is very glossy, and well bound. It can be highly recommended. No doubt subsequent texts will be of a similar high calibre.

—*Mark C. Wheelock.*

THE SECOND of a six volume work on *Cancer*[11] deals with the *Pathology of Malignant Tumours*. There are 33 chapters with 30 separate authors. Most of the writers are well known and internationally famous.

A variety of opinions is presented with a fairly even flow of concepts. The first 3 sections deal successively with general pathology of malignant tumors, biologic characteristics of neoplasia, and modes of spread of malignant tumors. All remaining chapters deal with cancer in the respective organs, systems, and tissues. Macrophotographs and microphotographs are carefully selected and produced and illustrate the lesions thoroughly. Tables, where indicated, are used judiciously. The bibliographies, at the end of each chapter, are modern and still do not ignore some of the classic references of the past. In perusal of the text, the reader must keep in mind that only malignant lesions are presented; in other words, this is about cancer in the generic form. Distribution of space is in relation to the frequency of the malignant neoplasm in the organs or tissues—less for parathyroid and adrenal, more for stomach and lung. The level of all segments is so high that no particular one or ones may be cited. This reviewer is well pleased with Volume II and recommends it for complete study or for occasional consultation. Both purposes are readily served. —*Mark C. Wheelock.*

[11] CANCER. Edited by Ronald W. Raven, O.B.E.(Mil.), T.D., F.R.C.S. Vol. II. Part II. PATHOLOGY OF MALIGNANT TUMOURS. 666 pages, 357 illustrations. $18.00. London: Butterworth & Co., Ltd., 1958.

BOOKS RECEIVED

BOOKS received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

INTERNATIONAL FERTILITY ASSOCIATION. PROCEEDINGS OF THE SECOND WORLD CONGRESS ON FERTILITY AND STERILITY. Edited by G. Tesauro. Vols. I and II. 2948 pages, 816 illustrations. Naples: Institute of Clinical Obstetrics and Gynecology, Naples University, 1957.

HYPERTENSION; THE FIRST HAHNEMANN SYMPOSIUM ON HYPERTENSIVE DISEASE. Edited by John H. Moyer, M.D. Assisted by John R. Beem, M.D., Robert Bower, M.D., Joseph R. DiPalma, M.D., Arthur Grollman, M.D., William Likoff, M.D., and Lewis C. Mills, M.D. 790 pages, illustrated. Philadelphia and London: W. B. Saunders Co., 1959.

THE FUNCTIONS OF THE ENDOCRINE GLANDS. By Peter F. Hall, M.D., M.R.C.P., M.R.A.C.P. 290 pages, 77 illustrations. Philadelphia: W. B. Saunders Co., 1959.

ANGEWANDTE UND TOPOGRAPHISCHE ANATOMIE; EIN LEHRBUCH FUER STUDIERENDE UND AERZTE. By Prof. Dr. G. Töndury. 2nd ed. 578 pages, 411 illustrations. $18.80. Stuttgart: Georg Thieme Verlag, 1959.

OFFICE GYNECOLOGY. By J. P. Greenhill, M.D., F.A.C.S. 7th rev. enl. ed. 572 pages, 145 illustrations. $9.00. Chicago: The Year Book Publishers, Inc., 1959.

GENETICS, RADIOBIOLOGY AND RADIOLOGY PROCEEDINGS, MID-WESTERN CONFERENCE. By Wendell G. Scott, M.D., Chairman, and Titus Evans, Ph.D., Co-Chairman. 149 pages, illustrated. $5.50. Springfield, Ill.: Charles C Thomas, 1959.

ORTHOPEDIC NURSING PROCEDURES. By Avice Kerr, R.N., B.A. 364 pages, illustrated. $4.75. New York: Springer Publishing Co., Inc., 1959.

A GUIDE TO ORTHOPAEDICS. By T. T. Stamm, M.B., B.S., F.R.C.S. 155 pages, 19 illustrations. $3.00. Springfield, Ill.: Charles C Thomas, 1959.

PRINCIPLES AND PRACTICE IN THE MANAGEMENT OF SURGICAL PATIENTS: A TEXTBOOK FOR THE USE OF INTERNES, HOUSE-SURGEONS, POST-GRADUATES AND JUNIOR PRACTITIONERS OF SURGERY. By A. Venugopal Mudaliar, M.S., F.A.C.S., F.I.C.S. 500 pages, illustrated. Rs. 20/-or 30 sh. Madras, India: S. Bhattacharya & Co., 1959.

DIE BEHANDLUNG ENTZUENDLICHER GENITALERKRANKUNGEN DER FRAU. By Prof. Gustav Doderlein. 148 pages, illustrated. DM 15.20. Leipzig: Georg Thieme, 1959.

ORTHOPAEDICS: PRINCIPLES AND THEIR APPLICATION. By Samuel L. Turek, M.D. 906 pages, 600 illustrations, 53 in color. $22.50. Philadelphia and Montreal: J. B. Lippincott Co., 1959.

A TEXTBOOK OF MEDICINE. Edited by Russell L. Cecil, M.D., and Robert F. Loeb, M.D. 10th ed. 1665 pages, 182 illustrations. Philadelphia and London: W. B. Saunders Co., 1959.

SURGERY OF THE EAR. By George E. Shambaugh, Jr., M.D. 669 pages, 326 illustrations. Philadelphia and London: W. B. Saunders Co., 1959.

CANCER. Edited by Ronald W. Raven, F.R.C.S. Vol. V. Part IX. Radiotherapy. 425 pages, 136 illustrations. $18.00. London: Butterworth & Co. Ltd., 1959.

ATLAS OF TUMOR PATHOLOGY. Section VIII—Fascicle 31a, TUMORS OF THE URINARY BLADDER. By Nathan B. Friedman, M.D., and James E. Ash, M.D. Published by the Armed Forces Institute of Pathology under the Auspices of the Subcommittee on Oncology of the Division of Medical Sciences of the National Academy of Sciences—Research Council. 82 pages, 86 illustrations. $1.00. Washington, D. C.: Armed Forces Institute of Pathology, 1959.

PRINCIPLES OF PERIPHERAL VASCULAR SURGERY. By S. Thomas Glasser, M.D., C.M., F.A.C.S., F.A.C.A. 410 pages, illustrated. Philadelphia: F. A. Davis Co., 1959.

TREATMENT OF LUNG CAVITIES AND ENDOBRONCHIAL TUBERCULOSIS; WITH SPECIAL REFERENCE TO TREATMENT IN MALAYA. By Beryl E. Barsby, M.D., M.R.C.P. 147 pages, 46 illustrations. $4.75. Edinburgh and London: E. & S. Livingstone Ltd., 1959; Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

AMERICAN COLLEGE OF SURGEONS

NEWELL W. PHILPOTT, Montreal, Canada, *President*

OWEN H. WANGENSTEEN, Minneapolis, *President-Elect*

PRELIMINARY PLANS FOR THE 45TH CLINICAL CONGRESS CONVENTION HALL, ATLANTIC CITY, NEW JERSEY SEPTEMBER 28 TO OCTOBER 2, 1959

IN THIS ISSUE, for your earlier consideration, an advance outline of nine Postgraduate Courses is listed, giving chairmen, moderators, lecturers, and subjects. Courses will appear in full in the final program. Because seating is limited for these classes it is advisable to register for the course of your choice as soon as possible. Fee is $5.00.

Preoperative and Postoperative Care

CHAMP LYONS, Birmingham, *Chairman*
Tuesday through Friday, 8:30–11:30 a.m.

PROBLEMS OF EXTRACORPOREAL PERFUSION

JOHN H. GIBBON, JR., Philadelphia, Moderator.

Rate Versus Pressure as an Index of the Adequacy of Perfusion. RICHARD A. THEYE, JOHN W. KIRKLIN, Rochester, Minnesota.

Metabolic Acidosis. GEORGE H. A. CLOWES, JR., Cleveland.

Pulmonary Complications. JOHN Y. TEMPLETON III, Philadelphia.

Cardiac Pacemakers. WILLIAM W. L. GLENN, New Haven.

POSTTRAUMATIC RENAL INSUFFICIENCY

FRANCIS D. MOORE, Boston, Moderator.

Blood and Urinary Findings: Early Management. SAMUEL R. POWERS, JR., Albany.

Differential Diagnosis of Posttraumatic Oliguria. JOHN M. HOWARD, Philadelphia.

Mild and Atypical Forms; Treatment Without Dialysis; Recovery Phase in Tubular Necrosis. JOHN P. MERRILL, Boston.

Indications for and Limitations on the Use of the Artificial Kidney. PAUL E. TESCHAN, San Antonio.

HEPATIC INSUFFICIENCY

DAVID V. HABIF, New York, Moderator.

Dietary Management in Hepatic Insufficiency. ARTHUR J. PATEK, JR., New York.

Portal Hypertension. LOUIS M. ROUSSELOT, New York.

Episodic Stupor. THOMAS B. PATTON, Birmingham, Ala.

Medical and Surgical Treatment of Ascites. WILLIAM V. MCDERMOTT, JR., Boston.

BLOOD TRANSFUSIONS AND ALLIED PROBLEMS

FRANK B. BERRY, Washington, D. C., Moderator.

Programs for Increased Use of All Blood Components. HENRY T. GANNON, Washington, D. C.

Blood Component Therapy (Use of Packed Red Cells, Frozen Cells, Platelets, Fibrogen, and Clotting Components). JAMES L. TULLIS, Brookline, Massachusetts.

Blood Programs in an Overseas Theatre. DOUGLAS B. KENDRICK, Headquarters U.S. Army, Europe.

Special Transfusion Problems. IVAN W. BROWN, JR., Durham, North Carolina.

Gastrointestinal Disease

ROBERT T. TIDRICK, Iowa City, *Chairman*
Tuesday through Friday, 8:30–11:30 a.m.

CURRENT CONSIDERATIONS IN ESOPHAGEAL SURGERY

F. HENRY ELLIS, Rochester, Minnesota, Moderator.

Current Concepts of Esophageal Function. F. HENRY ELLIS.

Achalasia, Diffuse Esophageal Spasm, and Current Treatment. WILLIAM M. TUTTLE, Detroit.

Importance of the Cardioesophageal Angle. DAVID H. WATKINS, Denver.

Hypopharyngeal and Esophageal Diverticula. DONALD B. EFFLER, Cleveland.

Esophageal Carcinoma. Resection. Radiation. IRVING M. ARIEL, New York.

THE SURGICAL TREATMENT OF ACID-PEPTIC DISEASE

EDWIN H. ELLISON, Milwaukee, Moderator.

Introduction: The "Ideal" Ulcer Operation in Light of Current Knowledge of Gastric Physiology. EDWIN H. ELLISON.

Review of Current Status in Surgical Treatment of Duodenal Ulcer. LYLE J. HAY, Minneapolis.

Vagectomy with Outlet Alteration. EDWARD R. WOODWARD, Gainesville, Florida.

Vagectomy with Hemigastrectomy or with Antrectomy. EDWIN H. ELLISON.

Preparation for Operation of the Patient with Severe Pyloric Obstruction for Operation. HENRY T. RANDALL, New York.

Free Perforation. JOHN R. PAINE, Buffalo.

Mortality and Morbidity in Peptic Ulcer Surgical Treatment. BENTLEY P. COLCOCK, Boston.

SMALL INTESTINE

ARNOLD J. KREMEN, Minneapolis, Moderator.

Introduction: Functional Considerations in Resection and Side-Tracking of Small Intestine. ARNOLD J. KREMEN.

Current Concepts of Postsurgical Malabsorption Syndromes and Tests of Malabsorption. PARKER VANAMEE, New York.

Jejunal and Ileal Diverticulosis. EDWARD S. JUDD, Rochester.

Small Intestinal Tumors; Malignant and Benign. E. LEE STROHL, Chicago.

Repeated Obstruction of Small Intestine. Prevention of Adhesions and Obstruction. Current Status of Plication Procedures and Treatment of Recurrent Obstructions. GORDON K. SMITH, Los Angeles.

Intestinal Angina: Status of Diagnostic Procedures, Endarterectomy, and Resections of Stenotic Segments of Mesenteric Arteries. ROBERT S. SHAW, Boston.

COLON, RECTUM, AND ANUS

CHARLES W. MAYO, Rochester, Minnesota, Moderator.

Adenomatous Polyps and Cancer. WILLIAM D. HOLDEN, Cleveland; C. NAUNTON MORGAN, London.

Place of the Rectum, Anus, and Sphincter-Sparing Operation. B. MARDEN BLACK, Rochester, Minnesota.

Use of Ancillary Measures (Chemocancerocidal Agents and Radiant Energy) in Treatment. ROBERT C. HICKEY, Iowa City, and ROALD N. GRANT, St. Albans, New York.

Requirements of Adequate Cancer Operation (Colon, Rectum, and Anus). CHARLES W. MAYO and Panel.

Diseases of the Liver, Biliary Tract, and Pancreas

HARWELL WILSON, Memphis, *Chairman*

Tuesday through Friday, 8:30–11:30 a.m.

GALLBLADDER AND BILE DUCTS

HARWELL WILSON, Memphis, Moderator.

Cholecystitis and Cholelithiasis. J. ENGLEBERT DUNPHY, Portland, Oregon.

Differential Diagnosis of Jaundice. EDWARD H. STORER, Memphis.

Cholangiography and Cholecystography. R. KENNEDY GILCHRIST, Chicago.

Common Duct Stone. HENRY N. HARKINS, Seattle.

Stricture of the Common Bile Duct. HARWELL WILSON.

LIVER AND SPLEEN

JAMES D. RIVES, New Orleans, Moderator.

Liver Abscess. JAMES D. RIVES.

Subphrenic and Subhepatic Abscess. CLARENCE E. GARDNER, JR., Durham.

Massive Hepatic Resection for Large Benign Tumors. HARWELL WILSON.

Surgical Treatment of Malignant Tumors in the Liver. JOHN T. REYNOLDS, Chicago.

Indications for Splenectomy. GEORGE G. FINNEY, Baltimore.

PANCREAS

ROBERT M. ZOLLINGER, Columbus, Moderator.

Pancreatitis. ROBERT M. ZOLLINGER.

Surgical Treatment of Chronic Pancreatitis. ROBERT J. COFFEY, Washington, D. C.

Cysts of the Pancreas. WILLIAM R. SANDUSKY, Charlottesville.

Carcinoma of the Pancreas. JONATHAN E. RHOADS, Philadelphia.

Islet Cell Tumors of the Pancreas. MILTON R. PORTER, New York.

HEPATIC COMA AND PORTAL HYPERTENSION

EDWARD H. STORER, Memphis, Moderator.

Biochemical Defects in Patients with Hepatic Coma. HAROLD A. HARPER, San Francisco.

Diagnosis and Treatment of Hepatic Coma. BEN EISEMAN, Denver.

Splenoportography. FRANCIS C. JACKSON, Pittsburgh.

Emergency Surgical Treatment of Bleeding Esophageal Varices. ROBERT R. LINTON, Brookline.

Indications for and Long-Term Results of Splenorenal and Portacaval Shunts. ARTHUR H. BLAKEMORE, New York.

Cardiovascular Surgery

HENRY T. BAHNSON, Baltimore, *Chairman*

Tuesday through Friday, 8:30–11:30 a.m.

PORTAL HYPERTENSION AND ANEURYSMS

ORMAND C. JULIAN, Chicago, Moderator.

Physiology or Portal Hypertension from the Surgeon's Viewpoint. BEN EISEMAN, Denver.

Direct Suture of Esophageal Varices. GEORGE CRILE, JR., Cleveland.

Portacaval Shunt. C. STUART WELCH, Albany.

Use of the Tube and Supportive Measures in Acute Hemorrhage from Varices. ARTHUR H. BLAKEMORE, New York.
Arterial Prostheses. W. STERLING EDWARDS III, Birmingham.
Treatment of Thoracic Aneurysms. HENRY T. BAHNSON, Baltimore.
Treatment of Abdominal Aneurysms. WILLIAM S. DYE, JR., Chicago.

PERIPHERAL VASCULAR DISEASE
OSCAR CREECH, JR., New Orleans, Moderator.
Thromboembolism and Acute Phlebitis. HOWARD MAHORNER, New Orleans.
Problems in Lymph Stasis. T. G. BLOCKER, JR., Galveston.
Arterial Embolism and Acute Thrombosis. RICHARD WARREN, Boston.
Inflammatory and Vasospastic Vascular Disease. F. A. SIMEONE, Cleveland.
Arterial Injury. FRANK C. SPENCER, Baltimore.
Methods Other than Direct Attack in Arterial Disease. EDWARD A. EDWARDS, Boston.
Direct Surgery for Arterial Disease of Lower Extremities. WILEY F. BARKER, Los Angeles.
Extracranial Cerebral Vascular Disease. E. STANLEY CRAWFORD, Houston.
Renal Arterial Disease. PAUL T. DECAMP, New Orleans.
Peripheral Arterial Aneurysms. GEORGE C. MORRIS, JR., Houston.

OPEN HEART SURGERY
ANDREW G. MORROW, Bethesda, Moderator.
Diagnosis of Congenital Heart Disease. JOSEPH R. LATSON, Houston.
Special Diagnostic Methods. EUGENE BRAUNWALD, Bethesda.
Basic Physiology of Cardiopulmonary Bypass. JOHN H. GIBBON, JR., Philadelphia.
Hypothermia and Its Use. IVAN W. BROWN, JR., Durham.
Pathological Anatomy of Isolated Ventricular Septal Defect and Tetralogy of Fallot. MAURICE LEV, Chicago.
Ventricular Septal Defect. DWIGHT C. MCGOON, Rochester, Minnesota.
Tetralogy of Fallot. DENTON A. COOLEY, Houston.
Atrial Septal Defect and Anomalous Venous Return. F. JOHN LEWIS, Chicago.
Selection of Patients with Pulmonary Hypertension for Operation. FRANK GERBODE, San Francisco.

ACQUIRED HEART DISEASE
ALFRED BLALOCK, Baltimore, Moderator.
Coronary Artery Disease. DAVID C. SABISTON, JR., Baltimore; ROBERT P. GLOVER, Philadelphia; JACK A. CANNON, Los Angeles; ARTHUR VINEBERG, Montreal.
Cardiac Arrest. G. RAINEY WILLIAMS, Oklahoma City.
Pathological Anatomy of Aortic and Mitral Valvular Disease. JULIO C. DAVILA, Philadelphia.
Mitral Stenosis. DWIGHT E. HARKEN, Boston.
Mitral Insufficiency. HENRY T. NICHOLS, Philadelphia.
Aortic Stenosis. WILLIAM H. MULLER, JR., Charlottesville.
Aortic Insufficiency. C. WALTON LILLEHEI, Minneapolis.

Internal Fixation and Operative Treatment of Fractures

WILLIAM H. CASSEBAUM, New York, *Chairman*
Tuesday through Friday, 8:30–11:30 a.m.

ADVANTAGES, DISADVANTAGES, AND INDICATIONS
PRESTON A. WADE, New York, Moderator.
Historical Review. SIR REGINALD WATSON-JONES, London.
Advantages, Indications, and Timing of Operative Treatment. HARRISON L. MCLAUGHLIN, New York.
Disadvantages of Internal Fixation and Their Avoidance. CHARLES S. NEER II, New York.
Operative Reduction and Internal Fixation of Fractures in Children. WALTER P. BLOUNT, Milwaukee.
Fractures Which Demand Internal Fixation or Operative Reduction. OSCAR P. HAMPTON, JR., St. Louis.

MECHANICAL PRINCIPLES
SIR REGINALD WATSON-JONES, London, Moderator.
Characteristics of Metals Suitable for Internal Fixation. The Metallurgy of Internal Fixation Appliances. Factors of Strength, Corrosion, Inertness, Pliability, Recoil, Fatigue, and Breaking. ALBERT B. FERGUSON, JR., Pittsburgh.
Principles of Carpentry and Mechanics as Related to Internal Fixation of Fractures. JAMES T. GREEN, Columbia, South Carolina.
A Critique of Internal Fixation Devices Now In Use. GEORGE J. CURRY, Flint.
Effect of Internal Fixation on Bone Healing. G. W. N. EGGERS, Galveston.
Internal Fixation with a Plastic Material; a Report on an Experimental Method. MICHAEL P. MANDARINO, Philadelphia.

INFECTION
FRANK E. STINCHFIELD, New York, Moderator.
Acute Infection. WILLIAM H. CASSEBAUM, New York.
Late Infection and Chronically Infected Bone. ALEXANDER P. AITKEN, Brookline.
Application of Internal Fixation: Open Fracture and Operative Treatment. JESSE W. MAHONEY, New York; Internal Fixation by Bone Plating. CARTER R. ROWE, Boston; Intermedullary Nails, Angle Devices. PRESTON A. WADE, New York.

APPLICATION OF INTERNAL FIXATION
WILLIAM H. CASSEBAUM, New York, Moderator.
Fixation with Multiple Pins and External Appliances. THOMAS B. QUIGLEY, Boston.
Malleable and Rigid Wires in Hand and Other Fractures. FREDERICK M. SMITH, Falmouth.
Angle Devices for Hips and Condyles of Femur. CARL E. BADGLEY, Ann Arbor.

Spine Fractures and Operative Treatment. HAROLD B. BOYD, Memphis.
A Summary, Philosophy and Wisdom. SIR REGINALD WATSON-JONES, London.

Gynecology and Obstetrics

BERNARD J. PISANI, New York, *Chairman*
Monday through Thursday, 8:30–11:30 a.m.

CERVICAL MALIGNANCY
LANGDON PARSONS, Boston, Moderator.
Clinical Investigation. HENRY C. MCDUFF, Providence.
Radiation Treatment. GILBERT H. FLETCHER, Houston.
Operative Treatment. HOWARD ULFELDER, Boston.
Combined Treatment. CHARLES S. STEVENSON, Detroit.
Complications of Treatment. C. BERNARD BRACK, Baltimore.

RECONSTRUCTIVE GYNECOLOGY
CLYDE L. RANDALL, Buffalo, Moderator.
Ovarian Resection. GEORGE P. HECKEL, Rochester, New York.
Tubal Reconstruction. WILLIAM J. MULLIGAN, Brookline.
Uterine Fibroids. ALLAN C. BARNES, Cleveland.
Uterine Prolapse. LAMAN A. GRAY, Louisville.
Stress Incontinence. C. PAUL HODGKINSON, Detroit.

OBSTETRICAL PROBLEMS IN THE SECOND TRIMESTER
BENJAMIN TENNEY, Boston, Moderator.
Uterine Bleeding, C. LEE BUXTON, New Haven.
Intrauterine Fetal Death. WILLIAM B. STROMME, Minneapolis.
Ectopic Pregnancy. H. HUDNALL WARE, JR., Richmond.
Incompetent Cervical Os. H. L. RIVA, Colonel, Washington, D. C.
Placental Abnormalities. J. EDWARD HALL, Brooklyn.

OBSTETRICAL EMERGENCIES AT TERM
EDWARD G. WATERS, Jersey City, Moderator.
Eclampsia and Fulminating Pre-Eclampsia. A. CHARLES POSNER, New York.
Repeat Cesarean Section and Rupture of Uterus. GORDON W. DOUGLAS, New York.
Shock and Coagulating Defects. SEYMOUR L. ROMNEY, New York.
Placental Bleeding (Previa and Separation). STANLEY M. BYSSHE, New York.
Anesthesia. CHARLES E. FLOWERS, JR., Chapel Hill.

Athletic Injuries

DONALD B. SLOCUM, Eugene, Oregon, *Chairman*
Tuesday through Friday, 8:30–11:30 a.m.

JACK C. HUGHSTON, Columbus, Georgia, Moderator.
Purpose and Scope. DONALD B. SLOCUM, Eugene.
The Physical Basis for Restriction from Athletics: Pediatric Aspects. THOMAS E. SHAFFER, Columbus, Ohio.
Orthopedic Aspects. HOWARD A. MOLTER, Eugene.
Technique of Field Examination: Diagnosis and Emergency Treatment of Athletic Injuries. CHARLES J. FRANKEL, Charlottesville.
The Athletic Trainer: The Trainer's Viewpoint on Training and Conditioning in the Prevention of Athletic Injuries. HOWARD WAITE, Pittsburgh.
Athletic Protective Equipment: a Summary and Demonstration of Existing Protective Equipment, Its Use and Misuse, and a Review of Current Investigations in the Field. ALEXIUS RACHUN, Ithaca.

HOWARD A. MOLTER, Eugene, Oregon, Moderator.
Injuries to the Trunk and Head:
Maxillofacial Injuries. WILLIAM L. WHITE, Pittsburgh. Neurologic Aspects. DONALD L. STAINSBY, Eugene, Oregon.
Orthopedic Aspects. EDMOND J. MCDONNELL, Baltimore.
Tendon Injuries in Sports: the Mechanism, Diagnosis, and Treatment. BRUCE J. BREWER, Milwaukee.
Mechanics of Football Injuries. A Pictorial Description of Football Injuries Together with a Summary of the Injury Types Resulting from Each Situation. DONALD B. SLOCUM.

THOMAS B. QUIGLEY, Boston, Moderator.
Sports Injuries After 30. DANIEL H. LEVINTHAL, Beverly Hills.
Ski Injuries: Mechanism, Diagnosis, and Treatment. MACK L. CLAYTON, Denver.
Injuries to the Knee and Thigh:
Treatment of Fresh Cartilage and Ligamentous Injuries of the Knee. BRUCE J. BREWER, Milwaukee.
Treatment of Old Ligamentous Injuries of the Knee. DONALD E. STARR, Vancouver.
Fractures and Orthopedic Conditions About the Knee and Thigh. DANIEL H. LEVINTHAL.

INJURIES TO THE UPPER EXTREMITY
DONALD E. STARR, Vancouver, Moderator.
Injuries to the Shoulder and Arm in the Throwing Sports: Mechanism, Diagnosis, and Treatment. JAMES E. BATEMAN, Toronto.
Injuries to the Shoulder and Arm in Contact Sports: Mechanism, Diagnosis, and Treatment. S. BENJAMIN FOWLER, Nashville.
Injuries to the Elbow, Forearm, and Hand: Mechanism, Diagnosis, and Treatment. WILLIAM M. DEYERLE, Richmond.

INJURIES TO THE ANKLE
JAMES E. BATEMAN, Toronto, Moderator.
Ankle Sprain; Mechanism, Diagnosis, and Treatment. THOMAS B. QUIGLEY, Boston.
Fractures of the Leg and Ankle; Mechanism, Diagnosis, and Treatment. JACK C. HUGHSTON, Columbus, Georgia.
Soft Tissue Trauma and Fractures to the Foot; Mechanism, Diagnosis, and Treatment. ROBERT G. THOMPSON, Chicago.

Surgical Aspects of Pulmonary Disease

ROBERT R. SHAW, Dallas, *Chairman*
Monday through Thursday, 1:30–4:30 p.m.

THE SURGEON AND RESPIRATORY FUNCTION

EDWARD A. GAENSLER, Boston, Moderator.

Pulmonary Physiology and Surgical Practice. EDWARD A. GAENSLER.

Recent Advances in the Evaluation of Pulmonary Function:

Oximetry. WILLIAM E. ADAMS, Chicago.

Polarographic Determination of Blood Oxygen Tension. T. RICHARD WATSON, Hanover, New Hampshire.

Carbon Monoxide Techniques for Measurement of Pulmonary Diffusing Capacity. DAVID W. CUGELL, Chicago.

Pulmonary Compliance and Resistance Studies. INGA LINDGREN, Boston.

Surgery for the Relief of Chronic Pulmonary Insufficiency:

Decortication. T. RICHARD WATSON, Hanover, N. H.

Tracheobronchial Reconstruction. ROBERT R. SHAW, Dallas.

Neural Surgery for Asthma and Emphysema. KARL P. KLASSEN, Columbus, Ohio.

SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS

HARRY E. WALKUP, Oteen, N. C., Moderator.

Chemotherapy and Timing of Surgery. WILLIAM S. SCHWARTZ, Oteen, North Carolina.

Excisional Therapy. JOHN T. MENDENHALL, Madison.

Role of Collapse Therapy. JOHN D. STEELE, JR., San Fernando.

Surgical Drainage and Decortication in the Management of Pleural Complications. HARRY E. WALKUP, Oteen, N. C.

SURGERY FOR MYCOTIC DISEASES OF THE LUNGS

JOHN W. POLK, Springfield, Missouri, Moderator.

Medical Aspects of Mycotic Diseases of the Lungs. MICHAEL L. FURCOLOW, Kansas City, Kansas.

Surgical Aspects of Mycotic Diseases of the Lungs: Blastomycosis. FELIX A. HUGHES, JR., Memphis. Histoplasmosis. JOHN W. POLK, Springfield, Missouri. Coccidioidomycosis. BYRON H. EVANS, Fresno.

BRONCHOGENIC CARCINOMA

JULIAN JOHNSON, Philadelphia, Moderator.

Present Place of the Routine Chest Survey in the Detection and Treatment of Bronchogenic Carcinoma. KATHARINE R. BOUCOT, Philadelphia.

An Aggressive Viewpoint in the Surgical Treatment of Carcinoma of the Lung. J. MAXWELL CHAMBERLAIN, New York.

A Conservative Viewpoint in the Surgical Treatment of Carcinoma of the Lung. JULIAN JOHNSON, Philadelphia.

Use of Irradiation in Treatment of Carcinoma of the Lung. J. E. MILLER, Dallas.

Use of Chemotherapy in Treatment of Carcinoma of the Lung. PAUL C. ADKINS, Washington, D. C.

Recent Advances in Pediatric Surgery

C. EVERETT KOOP, Philadelphia, *Chairman*
Tuesday through Friday, 8:30–11:30 a.m.

GENERAL CONSIDERATIONS

C. EVERETT KOOP, Moderator.

Factors Affecting Success and Failure in Pediatric Surgery. HARRY C. BISHOP, Philadelphia.

Practical Applications of Embryology to Surgery of the Newborn. WILLIAM H. SNYDER, JR., Los Angeles.

Anesthesia and Temperature Control: Expectations and Limitations. LEONARD BACHMAN, Philadelphia.

Technical Differences Between Surgery of Infancy and That of Adult Life. ALEXANDER H. BILL, JR., Seattle.

The Surgeon's Role in Diagnosis and Management of Jaundice in Infancy. LAWRENCE K. PICKETT, Syracuse.

SURGERY OF THE INTESTINAL TRACT

C. EVERETT KOOP, Moderator.

Roentgen Examination of the Bowel. JOHN W. HOPE, Philadelphia.

Duodenal Obstruction. J. ROGER NEWSTEDT, Cincinnati.

Technical Aspects of the Management of Ileal and Jejunal Atresia. CLIFFORD D. BENSON, Detroit.

Obstruction of the Colon. H. WILLIAM CLATWORTHY, JR., Columbus, Ohio.

Imperforate Anus. ORVAR SWENSON, Boston.

Intussusception. THOMAS V. SANTULLI, New York.

SURGERY OF THE CHEST

C. EVERETT KOOP, Moderator.

Roentgen Examination of the Chest. JOHN W. HOPE, Philadelphia.

Staphylococcal Pneumonia with Pyopneumothorax; a Surgical Emergency in Infancy. CHARLES L. MINOR, Philadelphia.

Management of Diaphragmatic Hernia in the Newborn. WILLIAM L. RIKER, Chicago.

Respiratory Emergencies in the Newborn. LESTER W. MARTIN, Cincinnati.

Lesions of the Mediastinum. R. W. PAUL MELLISH, Philadelphia.

MISCELLANEOUS PROBLEMS IN PEDIATRIC SURGERY

C. EVERETT KOOP, Moderator.

Management of Bleeding from the Rectum. HARVEY E. BEARDMORE, Montreal.

Special Considerations in the Management of Burns in Children. BERNARD J. SPENCER, Minneapolis.

Tumors in Children. WILLIAM B. KIESEWETTER, Pittsburgh.

Surgical Management of Congenital Anomalies of the Neck. TAGUE C. CHISHOLM, Minneapolis.

Portal Hypertension. LUKE W. ABLE, Houston.